Changes in Anterior Segment Configuration in Primary Angle-closure Suspects after Prophylactic Laser Iridotomy

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I, Yuzhen Jiang, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis accordingly.

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Abstract

Aims

To determine the immediate and longitudinal changes in anatomical configurations of the anterior chamber angle in primary angle-closure suspects eyes treated and untreated by laser peripheral iridotomy (LPI). This research project also aims at investigating associations of angle configuration, dynamic iris behaviours and factors associated with outcomes of prophylactic LPI in primary angle-closure (PAC) suspects.

Methods

Study subjects were participants in a prospective randomised controlled clinical trial. Each participant was treated by LPI in one randomly selected eye, with the fellow eye serving as a control. Angle configuration and iris configuration were assessed in a masked fashion using gonioscopy and anterior segment optical coherence tomography (AS-OCT) before and at 2 weeks, 6 months, 18 months, 36 months and 54 months after LPI. Anatomical features of angle-related structures were assessed with a qualitative grading system using standard ultrasound biomicroscopy (UBM) images.

Results

Of the 889 PAC suspects who were included into the current study, 735 were women. At baseline, compared to males, female participants appeared to have narrower

gonioscopic angle width, wider range of appositional iridotrabecular contact, narrower limbal anterior chamber depth. In most of the eyes of primary angle-closure suspects in the current study, gonioscopic angle width measured in four quadrants followed the same sequence, namely: inferior > nasal > temporal > superior.

Compared to eyes with wide open angles after LPI, a greater proportion of eyes with angles which remained narrow after LPI had medium or thick overall iris thickness (*P* values≤0.009). Relatively more eyes with angles which remained narrow after LPI had anterior iris insertion, especially in the superior quadrant (P<0.001). Eyes with residual narrowing of angles after LPI also tended to have anteriorly positioned ciliary process (*P* values≤ 0.002).

No significant difference was found in baseline measures of angle configuration between treated and untreated eyes. At 2 weeks after LPI, the drainage angle on gonioscopy widened from a mean of 13.3^0 at baseline to a mean of 25.5^0 in treated eyes, which was also confirmed by significant increases in all AS-OCT angle width measures(*P*<0.001 for all variables). Between 2 weeks and 18 months following LPI, a significant decrease in angle width was observed over time in treated eyes (*P*<0.001 for all variables), although the change over the first 5.5 months was not statistically significant. In untreated eyes, angle width consistently decreased across all follow-up visits after LPI, with a more significant longitudinal trend for narrowing of angle configuration compared to treated eyes. In men and women, both treated and

untreated eyes experienced a slight but statistically significant increase at 36 months after LPI, and then decreased once again with time toward 54 months after LPI.

At baseline, in both men and women the cross-sectional area and volume of the iris significantly decreased when the illumination changed from light to dark (all differences were statistically significant, $P<0.001$). Two weeks after LPI, the relationship between iris cross-sectional area in dark and in light remained similar, although the magnitude of dynamic change in iris anatomy decreased significantly compared to the pre-LPI status.

Conclusions

Eyes with thicker overall or peripheral iris, more anterior insertion of the iris, and more anteriorly positioned ciliary body are more disposed to having persistent narrow angles following LPI. LPI resulted in remarkable increase in angle width of PAC suspects immediately after the procedure. However, this did not seem to change the trend for anterior chamber angle to narrow down over time, which was shown in our study cohort to be a shared feature in both treated and untreated eyes. The current research has also shown that decrease in illumination can result in significantly decreased iris cross-sectional areas in eyes of PAC suspects. This characteristic of iris dynamic behaviour in PAC suspects was compromised by the elimination of pupillary block in female angle-closure suspects.

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Personally Published Papers Pertinent to this Thesis

1. **Jiang Y,** Chang DS, Foster PJ, He M, Huang S, Aung T, Friedman DS. Immediate changes in intraocular pressure after laser peripheral iridotomy in primary angle-closure suspect. Ophthalmology. 2012 Feb;119(2):283-8.
2. **Jiang Y,** Chang DS, Zhu H, Khawaja AP, Aung T, Huang S, Chen Q, Munoz B, Grossi CM, He M, Friedman DS, Foster PJ. Longitudinal changes of angle configuration in primary angle-closure suspects: the Zhongshan Angle-Closure Prevention Trial. Ophthalmology. 2014 Sep;121(9):1699-705
3. **Jiang Y,** He M, Friedman DS, Khawaja AP, Lee PS, Nolan WP, Yin Q, Foster PJ. Associations between narrow angle and adult anthropometry: the Liwan Eye Study. Ophthalmic Epidemiol. 2014 Jun;21(3):184-9
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1. Background

1.1. Classification and Diagnostic Criteria of Primary Angle-closure

1.1.1. Two Major Types of Primary Glaucoma

It has been widely accepted over the past several decades that primary glaucoma consists of two major subtypes: primary open angle glaucoma (POAG) and primary angle-closure glaucoma (PACG).[1,2]

By biometric analysis of the anterior segments in eyes with glaucoma, Rosengren [3] was the first to quantitatively classify primary glaucoma into two categories: those symptomatic cases with shallower anterior chambers and relatively higher intraocular pressure (IOP), and those asymptomatic cases with anterior chambers of normal depth. A popular classification system at that time (the years around 1950s to 1960s) was to classify glaucoma into two subtypes: chronic simple glaucoma and closed-angle glaucoma. By then, chronic simple glaucoma was described by clinicians as presenting with elevated IOP at the presence of gonioscopically open anterior chamber angles (ACA), pathological cupping of the optic nerve head (ONH) (with or without loss of vision), as well as visual field loss associated with the optic neuropathy. The condition

was characterized by slow and asymptomatic insidious progression, and was often only discovered in routine tonometry or fundus examination. The control of IOP in ‘chronic simple glaucoma’ was believed to be helpful only at earlier stages of the disease and was felt by many clinicians to be no guarantee for stopping the progression of the disease. In contrast to the ‘chronic simple glaucoma’, another category, the ‘closed-angle glaucoma’, according to the concepts in 1960s, usually presented with episodes of acute visual loss, haloes and discomfort. Patients of this type of glaucoma were usually picked up by acute attacks of angle-closure with the above typical symptoms. As another distinct difference from “chronic simple glaucoma”, it was believed that effective IOP control can ensure the prevention of further damage to vision in the treatment of this disorder. [4] It is easy to tell from the aforementioned early classification that the typical form of PACG familiar to western ophthalmologists usually presents as acute or subacute symptomatic episodes. However, this impression or understanding was later found to be not well-grounded, especially among Asians. More recent prevalence studies have shown that over 75% of PACG patients never experienced acute attacks of primary angle-closure (PAC) [5] . The majority part of PACG is clinically presented in a chronic asymptomatic form.[5-11]

Although the two major types of primary glaucoma seem to be mutually exclusive, it was found in clinical practice that the history, symptoms, signs and course of disease development or progression of many cases could fail to fit in neither of the 2 categories. These cases were once named as “mixed glaucoma”, although consensus has not

been achieved in the definition of this term. In 1961, Abram[4] reported his investigation on 47 cases identified as “mixed glaucoma” out of 1861 cases by glaucoma specialists. He found that “mixed glaucoma”, which he defined as co-existence of the two types of primary glaucoma, was probably very rare and only 3 of the 47 cases may truly fit in this category. Most of the cases in Abram’s case series were found to fall in the following categories: (1) “chronic simple glaucoma” patients experiencing haloes as an atypical symptom; (2) occasional positive dark-room provocative test among ”chronic simple glaucoma” patients for unrecognizable reasons; (3) acute angle-closure attacks supervening on established “chronic simple glaucoma” with narrow but open ACA. Some of the cases presenting “narrow but open” ACA might be associated with topical treatment with miotic agents; (4) development of “chronic simple glaucoma” based on the damaged aqueous outflow pathway due to recurrent appositional contact between peripheral iris and the trabecular meshwork.

1.1.2. Diagnostic Criteria Primary Glaucoma

Appropriate and standardised case definition is crucial for the quality of epidemiological research [2] . Different diagnostic criteria and different definitions for narrow angles, occludable angles or angle-closure have been employed in previous epidemiological studies, a situation that makes it difficult to compare and combine prevalence data reported from studies carried out in various areas.

According to the widely-accepted definition published by the international consensus panel in 2002, regardless of the subtype, glaucoma can be diagnosed when three or more locations in the visual field, in a particular pattern, are found in visual field tests to be notably outside the limits of normal variability and when the cup-to-disc ratio of the same eye is larger than the level observed in 97.5% of the general population. [2]

In 2001, Foster et al proposed a new scheme for diagnosis of glaucoma in population-based prevalence surveys, which then turned out to be widely adopted in epidemiological studies and also frequently referred to as the ISGEO (International Society of Geographical and Epidemiological Ophthalmology) classification [2] . In this new classification system, characteristic pattern of structural pathology in ONH has been singled out as the feature that distinguishes glaucoma from other causes of visual morbidity. The term ”glaucoma” was then recommended to be reserved only for people with established, end organ, and probably visually significant damage, i.e. those who are found to have evidence of structural and functional glaucomatous damage to the optic nerve, presenting as enlargement of cup-to-disc ratio (CDR) in the ONH, which is combined with visual field defects that meet certain criteria. Considering the overlap between the CDRs in those with and without glaucomatous visual field defects, Foster and colleges [2] proposed the value above which 2.5% of the CDRs of normal population lie (i.e. the 97.5th percentile) as the upper limit of the normal CDR. Besides, the 97.5th percentile value for CDR asymmetry between an individual’s two eyes was also used as one of the criteria for abnormality. In this diagnostic scheme, glaucomatous visual

field defects were described as having the following characteristics: (1) asymmetrical across the horizontal midline in cases at early or moderate stages of disease development; (2) located in the mid-peripheral part of the visual field in early or moderate cases; (3) clustered in neighbouring test points; (4) reproducible on at least two occasions; (5) not explained by any other disease; (6) considered a valid representation of the subject's functional status based on performance indices. For special cases such as patients who cannot be properly cooperative in visual field examinations or those with significant media opacity which makes it impossible to acquire an adequately clear view of the fundus, Foster et al proposed the following alternative evidence of relatively lower levels but sufficient to make the diagnosis of glaucoma: (1) For cases in which reliable visual field test results could not be possibly acquired: a vertical CDR above the 99.5th percentile of the normal population range suggesting severe damage to ONH; (2) For eyes in which the optic nerve could not be possibly observed: an intraocular pressure (IOP) exceeding the 99.5th percentile of the normal population range or evidence of previous filtration surgery for the treatment of glaucoma.

1.1.3. Classification of Conditions Related to Primary Angle-closure

PACG was traditionally classified as acute and chronic angle-closure glaucoma, representing a simple classification logic based on presenting symptoms and the course of disease progression without putting much emphasis on the extent or severity

of angle-closure (including both appositional contact and pathological synechiae or adhesion) and the presence of glaucomatous optic neuropathy (GON) [12,13] . Some ophthalmologists also classify certain conditions as subacute angle-closure [13] . (1) The acute form of PACG was caused by sudden and complete or almost complete occlusion of the anterior chamber angle. The manifestations of acute primary angle-closure (APAC) include IOP elevation up to 60-70 mm Hg, blunt eye pain, brow ache, headache, nausea, vomiting, conjunctival congestion, corneal oedema from damage in the corneal endothelium, and glaukomflecken (subcapsular lens opacification) as a result of lenticular ischemia. This subtype of PACG can be remarkably detrimental to visual function. Its visual morbidity is primarily determined by the duration of attack with IOP elevation. [14] (2) Subacute angle-closure shared similar pathogenic basis with the acute subtype, although differing from APAC in the numerous episodes of attacks spontaneously remit with relatively milder symptoms. Subacute angle-closure cases typically present with a history of headaches, periorbital pain or eye pain that frequently occur at night or in the dark. More detailed medical history collection may reveal some other accompanying symptoms, such as red eye, circular halos around lights, blurred vision and asymmetric pupils [13] . (3) The chronic form of PACG, however, is characterized by chronically progressive angle-closure lacking typical symptoms. This subtype of PACG was once named by Lowe as “primary creeping angle-closure glaucoma” [15] . However, the gradual “creeping” closure is only one of the various patterns of angle-closure. The “creeping” angle-closure involves posterior trabecular meshwork first and then spread anteriorly. Alternatively, angle-closure can start by

involving both the anterior and posterior trabecular meshwork and then extend circumferentially. There can also be the co-existence of the above two patterns. [13]

Considering a predominant proportion of chronic asymptomatic cases, this traditional classification carries the risk of misclassifying conditions at risk of developing angle-closure (i.e. suspects) or those having experienced acute symptomatic episodes but functionally and pathologically intact for the diagnosis of PACG. In fact, over 60% of individuals suffering acute attacks of angle-closure recovered without having any visual field defects or abnormalities in the optic nerve head. [16] The visual morbidity attributable to PACG may be inaccurately evaluated if these cases were misclassified as PACG. Foster and colleagues [2] proposed a new classification system that puts emphasis on end organ (i.e. optic nerve) damage as the defining characteristic of glaucoma, and separate conditions related to angle-closure into 3 major categories: (1) primary angle-closure suspect (PACS); (2) primary angle-closure (PAC); (3) primary angle-closure glaucoma (PACG). Foster defined cases meeting gonioscopic criteria for narrow angles and with evidence of significant obstruction of the functional part of trabecular meshwork (either peripheral anterior synechiae (PAS) or elevated IOP) as PAC, whereas those with evidence of glaucomatous optic neuropathy were defined as PACG. PACS (or alternatively referred as PAC suspect in this thesis) was defined as eyes found to have occludable narrow angle configurations with normal optic disc, normal visual fields, normal IOP and no PAS. “Occludable angle” is a concept recently used in many epidemiological studies. Although to a certain degree, this terminology

reflects subjective judgment of the risk for angle-closure, the definition of “occludable angle” was based on observation under static gonioscopy. The drainage angle width was classified into “occludable” or “not occludable” by the range of visible posterior/pigmented trabecular meshwork (PTM) observed under static gonioscopy [17] . Although so far there is still no widely-accepted collective term, some studies have described all of the three aforementioned conditions as “angle-closure diseases” [18,19] or “primary angle-closure disease” (PACD). Sihota [20] recently pointed out that the ISGEO classification “did not take into account different grades of damage to the trabecular meshwork or optic nerve head, or acknowledge the importance of ocular hypertension in PAC”. For the purpose of reflecting the extent of trabecular meshwork and ONH dysfunction, she proposed a system classifying “primary angle-closure disease” into the following 4 stages: (1) PACD suspect: defined as eyes with occludable angle, i.e. an angle in which PTM is not visible in a circumference of 180° or above, or, an angle recess of less than 20°. (2) PACD I: eyes having occludable angles with definitive signs of angle-closure (mainly PAS, with other associated manifestations such as Irregular patchy pigmentation over the surface of the trabecular meshwork, iris atrophy, pupillary ruff atrophy, whorling of the iris, sector iris atrophy, or a generalised loss of iris pattern) in the absence of chronically elevated IOP or GON. (3) PACD II: eyes with occludable angles with definitive signs of angle-closure, and chronic IOP elevation after iridotomy as compared to either the population-based average IOP values or “the patient’s prior recorded IOP”. (4) PACD III: eyes having occludable angles with PAS, as well as GON and chronic IOP elevation after iridotomy.

The diagnostic criteria of acute primary angle-closure have been described differently in various clinical studies. In a study on changes in anterior segment morphology after LPI in Asian eyes, Gazzard and colleagues [21] diagnosed acute primary angle-closure on the basis of an occluded angle in the presence of an IOP of 25 mm Hg or greater when at least one of the following symptoms was present: (1) rapid onset of ocular pain or discomfort; (2) nausea and/or vomiting; or (3) subjective blurring of vision of recent onset or an antecedent episode of intermittent blurring with halos.

1.2. Prevalence of Primary Angle-closure in Different Ethnic Groups

According to an estimation based on data from epidemiological studies, there are approximately half a billion glaucoma patients around the world, about one third of whom have PACG. According to the definition of blindness by the World Health Organization (i.e, visual acuity in both eyes below 20/400), 25% of PACG go blind because of this disease. This proportion is about twice of the proportion of blind individuals among POAG patients. [22]

Multiple studies have shown a relatively higher prevalence of PAC or PACG in East Asia compared to other parts of the world, with asymptomatic chronic form of angle-closure being the most commonly seen form of the condition [8,9,18,23-31] . The Inuit

people of Alaska, Canada and Greenland, among whom the so far highest prevalence of PACG was reported, are believed to be descendants of early East Asians [24,32]. Clemmesen and Alsbirk reported that 86% of glaucoma diagnosed among Greenland Eskimos was PACG, which was identified as the leading cause of blindness among Greenland Eskimos. [33] The prevalence of angle-closure glaucoma in this population was reported to be 1.6% in males and 5.1% in females of the general population aged 40 years and above. In 1996, Foster et al [8] reported the outcomes of a population-based prevalence study in northern Mongolia. The population prevalence of manifest PACG was 1.4%. The prevalence of occludable angles (classified as PACS) was 6.4%. Later, another prevalence study in Chinese Singaporeans by the same team [9] reported a PACG prevalence of 1.3% (14 patients diagnosed in 1090 subjects examined). The prevalence reported from the Mongolia study was later proved to be close to the finding from another more recent study in Inner Mongolia using the ISGEO diagnostic criteria [28], which reported an age- and gender-standardised PACG prevalence of 1.42%. In China, based on findings from the epidemiological research in Mongolia and Singapore, Foster et al [34] estimated that around 9.4 million adults aged 40 years and older in China have GON. Of this number, 5.2 million (55%) are blind in at least one eye and 1.7 million (18.1%) are blind in both eyes. PACG is responsible for 91% of bilateral glaucoma blindness in China. The number of people with occludable drainage angle is around 28.2 million, of which 9.1 million have significant angle-closure indicated by PAS or raised IOP (classified as primary angle-closure, PAC). In an early population-based prevalence survey in Shanghai, east China, Guo et al [35] reported a PACG

prevalence of 0.55% among population aged 0 to 80+ years, which is equivalent to around 1.3% for the population aged over 40. However, this survey was not specifically designed for studying the prevalence of glaucoma, and the diagnostic criteria of PACG were not reported. Later in 1980s, Hu et al [36] carried out an epidemiologic investigation of glaucoma employing stratified random sampling in Shun-yi county of Beijing, Northern China. The prevalence of PACG among people age 40 years or above was reported to be 1.4%. PACG was reported to account for 79% of all glaucoma cases among the population aged above 20. Later, a prevalence study using stratified random sampling and ISGEO diagnostic criteria reported a 3.8% crude prevalence of all glaucoma among urban citizens in southern China, with the prevalence of PACG being 1.5% and the prevalence of POAG being 2.1%. [23] This ratio of POAG and PACG prevalence in southern China is slightly lower than the ratio (POAG to PACG, 2.6:1) reported from a more recent survey in northern China [26] . Another recent epidemiological study in northeast China [27] reported a relatively lower PACS prevalence of 4.7%, with the prevalence of PACG and PAC being 1.6% and 1.3% respectively. The PACG prevalence reported from recent studies in other areas of Asia varies from 0.39 to 2.0 [18,30,31,37].

There is an overwhelming clinical impression that the prevalence of POAG is higher than PACG in Europe and North America. Previous population-based prevalence studies found that PACG was only around 1/5 or even less as common as POAG in European-derived and African-derived populations. [6,38-43] The prevalence of PAC and

PACG reported from some previous epidemiological studies ranged from 0.04% to 0.4% [6,40,44,45] . A recent analysis by Day et al [29] has shown that PACG is more common than previously thought. Based on a review of epidemiological studies among European derived populations and using ISGEO definition [2] as the diagnostic criteria for PACG, it is estimated that the general prevalence of PACG among those of 40 years or older in European derived populations is approximately 0.4%. There are 130,000 people with PACG in the UK, 1.60 million in Europe and nearly 581,000 in the USA. Within the next 10 years, the number of PACG patients is predicted to increase by 19% in the UK, 9% in Europe, and 18% in the USA. [29]

1.3. Methods for the Assessment of Angle-closure

1.3.1. Grading of Limbal Anterior Chamber Depth

Although the result of oblique flashlight test has been proved to be closely related with gonioscopic findings [46,47] , the estimation of angle width by this method largely relies on the convexity of the iris-lens diaphragm. Hence, screening by oblique flashlight test takes the risk of being misinterpreted when the central anterior chamber is shallow in the presence of a large crystal lens, or when the angle is actually narrow with an unproportionally deep central anterior chamber in the presence of plateau iris configuration. [48] Limbal anterior chamber depth (ACD) has been suggested as a good surrogate for assessing angle width [49,50] . William van Herick described another method of limbal ACD assessment using slit-lamp biomicroscopy in 1968. [48] In this method, the limbal ACD was estimated by comparing the width of the slit beam as it traverses the anterior chamber to peripheral corneal thickness. The slit beam is placed perpendicular to the peripheral corneal surface and the angle opening is viewed at a 60-degree angle from the light beam. The slit-lamp beam should be as narrow as possible and the area of measurement is located just before the point of disappearance of the corneal-iris space at the periphery. The corneal section width (i.e. the peripheral corneal thickness) is used as the unit for estimating the anterior chamber angle width. According to van Herick's report, if the distance between the posterior cornea and the peripheral surface of the iris is equal to or greater than the section width of the corneal section under slit-

lamp biomicroscopy, gonioscopy will always show a wide-open, grade-4 angle. If the distance is equal to one half the width of the slit-lamp beam, which was defined by van Herick as Grade 3, angle-closure is very unlikely to occur. A width equal to one fourth of the corneal section width was defined as grade-2 angle, which was used as a cut-off line. Van Herick suggested that patients classified as having grade-2 angle in this test should undergo further gonioscopy. Finally, a distance less than one fourth of the width of corneal section was defined as grade-1 angle, which was described by van Herick as usually demonstrating a dangerously narrowed angle. Van Herick also compared the examination result of 400 eyes using this method and gonioscopy, and anterior chamber angle width assessed using his method agreed closely with gonioscopic evaluations. This method has been adopted by some large-scale clinical trials or epidemiological study as a crude screening tool to distinguish individuals who are possibly at greater risk of angle-closure [6,51] . In theory and ideally, this examination could be carried out by a non-ophthalmologist, although so far most of the screening programs involving van Herick grading still relied on ophthalmologists to carry out this test. [7] In fact, William van Herick, the person who introduced this method, also suggested in his initial report that several years' practice is needed for the examiner to be able to make an accurate assessment of limbal ACD using his grading system.

Tornquist [52] calculated limbal ACD using photographs acquired by a camera mounted on slit-lamp microscope and found that limbal ACDs of unoperated glaucomatous eyes were significantly shallower than those of non-glaucomatous controls. They also

discovered that the limbal ACD was significantly smaller in the upper part than in the lower part of the anterior chamber, which might be more associated with the difference in iris curvature rather than the small difference in peripheral corneal curvature. Chan et al[53] compared the central ACD, limbal ACD and ACA width measured by the Shaffer grading system in 110 phakic eyes, and found that both the average central ACD and limbal ACD increased in a linear manner with the Shaffer grading system of the width of the anterior chamber angle. Although they found the combination of central ACD and limbal ACD was most closely associated with Shaffer grades, the peripheral/limbal ACD measure by optical pachymetry was shown to be the best single factor in predicting the Shaffer grading of the width of the anterior chamber angle. Friedman et al [54] compared ocular biometry of the fellow eyes of unilateral acute angle-closure (AAC) cases, which are at especially high risk of developing AAC if left untreated [55-57] , with eyes of population-based control subjects in a Singaporean Chinese population using UBM and Scheimpflug photography. In the multiple logistic regression model, after adjusting for age and sex, patients with PACG were 19 times as likely to have a shallower limbal ACD (25%; 95% confidence interval, 8.3-45.2). Although the evaluation of limbal ACD using slit-lamp microscopy is less accurate than gonioscopy for assessing angle configuration, it can be very valuable as a screening method. [58]

1.3.2. Gonioscopy

In contrast to POAG, for which the diagnosis is classically based on IOP (although IOP

is no longer regarded as one of the diagnostic criteria according to the current understanding of glaucoma), GON and characteristic visual field defects [59] , the diagnostic identification of PACG and conditions that carry high risk of angle-closure largely relies on the examination of angle configuration. Among various examination techniques currently available for revealing angle anatomy, gonioscopy remains to be the mainstay examination and the widely accepted ”gold standard”.

The gonioscopic technique was first introduced in the late 19th century by Trantas, who physically indented the sclera in the purpose of observing ACA using a direct ophthalmoscope. However, the view was inevitably compromised by distorted cornea [60,61]. To overcome the total internal reflection due to the Snell’s law (light rays travelling from a more to a less dense reflection medium will be completely internally reflected when a certain critical angle is reached between the incident light ray and the vertical reference line), a contact lens allowing for direct viewing and a mirrored lens giving an indirect view were used to visualise ACA although the latter is most popular in current clinical settings [62] . In 1913, Salzmann applied contact lens in gonioscopy for the first time, and described the observation of PAS and blood in Schlemm’s canal owing to the improved view in gonioscopy. [61]

Direct gonioscopy (e.g. the Koeppe gonioscopic lens) has the advantages of giving a panoramic view, which possibly allows a better view of the relatively narrower ACA without causing artefacts in the view of angle configuration. However, the use of direct

gonioscopic lens can be inconvenient and time-consuming. The relatively lower magnification and the need for the patient to take supine position during the examination have driven ophthalmologists to abandon direct gonioscopic lens on most occasions of their routine practice. Indirect gonioscopy permits the use of higher magnification, better control of the sources of illumination, rapidity, and remarkable convenience to both the patient and the physician (when the Zeiss four-mirror lens is used: no coupling agent needed, hence no post-examination blur). The disadvantages of indirect gonioscopy include: it is in need of an excellent slit lamp, technically more difficult, hard to teach, and when performed improperly, it can lead to greater errors of interpretation than occur with incorrect direct gonioscopy. [63]

Among the currently widely used indirect gonioscopic lens which was introduced by Goldmann in 1938 [61] , the base curvature is a major feature that distinguishes different types [62] . The Goldmann lens is currently available with single, double and triple mirrors. The disadvantage with this type of lens is that the necessity of using coupling agent is sometimes unpopular for both patients and examiners. This has therefore discouraged some ophthalmologists from performing gonioscopy with Goldmann lens during routine examinations [13] .

Small diameter lens with small base curvatures can be directly fit on the corneal surface and compress the cornea centrally, a feature that facilitates dynamic gonioscopy. However, this may also lead to distortion of the view or widened ACA from

inadvertent compression on the cornea. This type of gonioscopy lenses, such as the Zeiss four-mirror gonioscopic lenses do not require coupling agent, which reduces blurring both the examiner's view into the eye and also the patient's vision following gonioscopy. Moreover, the examination procedure is slightly quicker, and less uncomfortable in the hands of skilful examiners. However, longer learning curve is needed for examiners to be able to gently position the lens over the corneal surface so as to avoid unintentional distortion of the angle. [64]

Larger lenses extending over the limbus to the sclera are less likely to distort the angle, but can possibly produce artefacts that make the ACA appear narrower by local compression over the area of the Schwalbe's line [65] , or wider when the lens is not centred on the cornea. One of the most widely used gonioscopy lenses at present is the Goldmann-style lens. Although the proper use of this type of lens require a coupling agent, its relatively wider base allows less chance to exert inadvertent pressure upon the cornea. The performance of Goldmann-style lenses (including the regular Goldmann gonioscopic lenses and the Magnaview lens) in dynamic gonioscopy has also been proved to be good in previous studies by using certain manipulation techniques to produce cornea indentation [8,9,66-68] and consequently open ACA by causing aqueous displacement [69] . This manipulation technique for dynamic gonioscopy with the Goldmann-style lens involves having the patient look in the direction of the mirror and pressing down over the lens to acquire a certain degree of indentation upon central cornea by locating the cornea under the rim of the lens.

It has been clearly shown in some recent studies that the appearance of ACA and the judgments of angle configuration can be greatly affected by illumination conditions, which shares similar mechanisms of changes in angle configuration under pharmacologic dilation. [38,70] Recently, it was clearly pointed out in the consensus document published by the Association for International Glaucoma Societies that static gonioscopy should be performed in a dark room using a 1-mm slit light beam with adequate illumination, and the configuration of ACA should be assessed in primary gaze with the patients looking straight forward [62] .

The Scheie Grading System

In 1957, Scheie [58] proposed a grading system based on the amount of angle structure which can be seen anterior to the iris surface. The grading systems introduced by Scheie and some other ophthalmologists all rely on several anatomical landmarks observed under gonioscopy [13] : (1) The Schwalbe's line: the end of Descemet's membrane, identified as the most anterior anatomical boundary of the angle structures. (2) The trabecular meshwork: divided into the anterior and posterior (frequently characterized by pigment deposition) parts, with the latter identified as the functional part for drainage of aqueous humour overlying Schlemm's canal. (3) The scleral spur: the attachment point of the ciliary body to the sclera, considered as the posterior boundary of the angle structures. The grade-0 angle in Scheie's grading system indicates that the ACA is wide open and the complete range of angle structures including the apex and the scleral spur could be readily seen. Grade I means that the angle is open but slightly narrow, and the last roll of the iris obscured part of the ciliary body. According to Scheie's description, in ACA of Grade-I width, the ciliary body (or, the ciliary band) is visible but the gonioscopist must exert effort to see over the iris root into the angle recess. Grade II means that nothing posterior to the trabecular meshwork was visible. Grade III indicates that the posterior portion of the trabecular meshwork was hidden, whereas Grade IV means that no structures posterior to Schwalbe's line can be seen and the ACA can be identified as being gonioscopically closed. Although Scheie's grading systems can help distinguish between narrow and wide angles, the difference between a closed and a narrow angle cannot be addressed

by using this system. Furthermore, Scheie also proposed to grade different meridians of the angle separately considering the variability of angle contour in different portions of its circumference. To facilitate provocative testing in eyes with excessive pigmentation and to determine the correlation between glaucoma and pigmentation of the angle, Scheie also introduced a scale for the qualitative description of pigmentation of the angle. Similar to the grading system introduced by Spaeth [63] later in 1970s, the posterior trabecular meshwork, which represents the crucial drainage pathway to the Schlemm's canal, was regarded as the most important portion of the angle in the grading of pigmentation. A set of schematic graphs showing pigmentation of the posterior trabecular meshwork graded from 0 to IV was included in the original publication introducing this grading system [58] . This grading system was used to predict the risk for acute attacks of primary angle-closure. Scheie claimed that he found the incidence of acute angle-closure and the rate of positive mydriasis tests was markedly higher in eyes with angles that were rated as grade III and grade IV. He also found higher incidence of glaucoma in eyes of grade IV pigmentation.

The Shaffer Grading System

For the purposes of diagnosis, classification, risk evaluation and progression monitoring, several grading schemes have been introduced for documenting findings observed under gonioscopy. The Shaffer grading system puts more emphasis on the angle of iris approach and provides a convenient method in comparing the widths of different anterior chamber angles. Measurement of the angle width is achieved through

the use of a gonioscopic lens together with the gonioscopist's subjective judgment of the amount of separation between two imaginary tangent lines drawn along the inner surface of the trabecular meshwork and to the anterior surface of the iris respectively.[5] [3] In the Shaffer grading system [71,72], the angle is graded in terms of the angular width of the angle: a wide, 40º approach results in a 'Shaffer 4' denomination; a slightly narrower 30º approach is 'Shaffer 3'; a narrow but well open angle of 20º is 'Shaffer 2'; an even narrower, but still open angle of 10º is classified as 'Shaffer 1'; a totally closed angle is 'Shaffer 0'. As Spaeth has pointed out, the problem with the Shaffer grading system is that one of the tangent lines used to access the angular width of the angle recess was not clearly defined and depends on the convexity of the anterior surface of the iris. With the various degrees of arching and bowing at different locations along the iris contour and among different individuals, it will be difficult for the examiners to determine which part of the iris to choose as the reference point for definition of the angularity.

The Spaeth Grading System

Later, in the early 1970s, Spaeth [61,63] summarised from his findings in previous studies and clinical experience that among angles thought narrow enough to occlude, only around 1 out of 10 will have "clinically apparent PACG". It is a crucial question in practice for glaucoma specialists to try to predict which narrow angle will close and which will not. As the shortcoming of the grading systems introduced by Scheie [58] and Shaffer [71,72] , Spaeth pointed out that the configuration of the anterior chamber angle

was too complex and varied to be accurately described on a single characteristic of the angle. Some more detailed characteristics of angle anatomy need to be observed and recorded in gonioscopy. In a study on the inheritance of occludable angles, Spaeth [64] compared gonioscopic findings in PACG cases with incidence of such findings in a large population without eye abnormalities as the controls. He found the anterior insertion was about 4 times as common in PACG cases as in controls. Moreover, a narrow approach to the drainage angle was seen 9 times more often and a marked anterior convexity of the peripheral iris was seen 11 times more frequently in the cases than in controls. He introduced a system of descriptive grading of ACA based on gonioscopic findings covering the following 3 main aspects [61,63] to characterise the configuration of the drainage angle: (1) The angular approach to the angle recess (using a line tangential to the inner surface of the trabecular meshwork as the base of the reference, the angle between this reference line and a tangent to the anterior surface of the iris approximately one-third of the distance from the most peripheral portion of the iris), as opposed to the angularity of the recess per se. Actually, in the Spaeth grading system, the configuration of the angle recess is accessed in two approaches: the angular approach to the angle recess and the width of the angle recess. The former, as mentioned above, is estimated in terms of degrees in 10° at a point slightly anterior to Schwalbe's line. The width of the angle recess, defined as the distance between the inner surface of the posterior trabecular meshwork and the anterior surface of the most proximal portion of the iris, is graded as: grade 0, contact between the two surfaces; grade 1, just detectable separation; grade 2, small but more

easily detectable separation; grade 3, moderate separation; and grade 4, wide recess. (2) The configuration of the peripheral iris, generally described as concave, relatively flat, or convex: The situations in which the iris appears to course quite regularly and smoothly from the recess without significant forward or backward arching, are described as ‘r’ (indicating ‘regular’). The situations, in which the iris dips posteriorly and present a concave or ‘queer’ appearance, are designated as ‘q’ (standing for ‘queer’, or concave). When the peripheral iris rises from its root with a rather sudden, steep, sharp convex curve, the iris configuration is classified as ‘s’ (indicating ‘steep’ or ‘sharp’). In regard to the overall contour of the iris, the convex bowing of the iris is graded as: none, minimal, mild, moderate, and marked. (3) The point where iris inserts onto the ciliary body or the internal lining of the eyeball: In the Spaeth grading system, the situations where the iris touches the corneal endothelium anterior to the trabecular meshwork around the Schwalbe’s line is designated as ‘A’ (indicating ‘anterior’). When the point of contact is behind the Schwalbe’s line in the area of the trabecular meshwork, the symbol is ‘B’ (indicating ‘behind’ the Schwalbe’s line). When the iris root is at the level of the scleral spur, the designation is ‘C’ (standing for the letter ‘c’ in ‘sclera’). The symbol ‘D’ (standing for ‘deep’) means a deep angle recess in which the anterior ciliary body is visible. The final category is designated as ‘E’ (standing for ‘extremely deep’), which indicates that the iris joins the ciliary body in an extremely posterior position, allowing an unusually wide range of ciliary body to be seen. If the designated symbol for iris insertion in the Spaeth grading system is surrounded with brackets, it means that the angle is so narrow that the actual insertion spot of the iris

root cannot be visualised in the course of normal gonioscopy, even by tilting the lens, adjusting illumination or having the patient change the gaze direction, and can only be observed with some pressure exerting on the Zeiss four-mirror gonioscopic lens in dynamic gonioscopy. The iris insertion locations observed in static gonioscopy are also indicated as “apparent” iris insertions, whereas those observed in dynamic gonioscopy are indicated as “true” iris insertions. Other characteristics introduced in Spaeth’s grading system as matters that should be paid special attention in gonioscopy include: the presence and type of the amount of iris processes; the amount of pigmentation in the posterior trabecular meshwork; and the nature of any adhesions [63]. The adding of iris contour into the grading system of anterior chamber angles was actually first proposed by Busacca [63,73], who divided his cases into 3 groups: the first group in which the iris surface was convex, in a curve similar to that of the cornea (i.e. convex iris configuration); the second in which the surface of the iris was essentially flat (i.e. flat iris configuration), and the third group in which a peripheral concavity was combined with a more central convexity (i.e. concave iris configuration). In the original grading system that Spaeth described in 1971 [63], the number of iris processes was indicated as: none, few or many. The type of iris process was designated as: ‘U’, for pilaster-like pigment fibres limited to the extreme depth of the recess; ‘V’, for those bridging the gap from the peripheral iris to the scleral spur or posterior trabecular meshwork; ‘W’, for those reaching to Schwalbe’s line. Apart from providing further information for a better understanding of the anatomy of the drainage angle, Spaeth also intended to apply this more detailed grading system to the investigation on genetic pathogenesis

of PACG based on the assumption that the above anatomical characteristics of the drainage angle might inherit independently. Apart from features of angle configurations, the Spaeth grading system also includes grading of pigmentation in the posterior trabecular meshwork. Pigment deposits in the posterior trabecular meshwork originate from the posterior iris pigment epithelium, starting to accumulate after puberty and increasing in amount throughout life. Increased pigmentation in the trabecular meshwork can be indicative of exfoliation, pigment dispersion syndrome, past inflammation, and transient angle-closure [13] . In the Spaeth grading system: grade 0 signifies no visible pigment; grade 1, just perceptible pigmentation; grade 2, a more definite but still mild amount; grade 3, a moderately dense band; and grade 4, a dense blackening of the posterior trabecular meshwork. The character, density and extent of pigmentation on Schwalbe's line were also categorised into the following grades: 0, trace, mild, moderate and severe. To ensure intra-grader and inter-grader reproducibility, standardised photos were used in some clinical practice and studies [74] .

Apart from subjective qualitative grading of angle width, another important purpose of performing gonioscopy for the diagnosis of PACG is to find out or rule out the existence of PAS, which has recently become one of the key distinctions between diagnostic criteria of PAC and PACS [75] . PAS, defined by some ophthalmologists as the pathological adhesions between the peripheral iris and structures anterior to its true insertion [13] , has also become one of the hot topics in PACG-related research. One of the questions that have aroused enormous interest is: what anatomical or functional

factors can lead to the development of PAS in eyes with narrow angles. In an early report on pigment changes in the anterior segment in primary glaucoma, Barkan [76] described one of the pigment disturbance varieties as 'the trabecular pigment bands that occur secondarily following congestive episodes associated with angle-closure, prolonged contact of the root of the iris with the angle wall, or after surgery', which was summarised by Barkan as "the mechanical derangement in the angle and to the characteristic pressure-producing changes (seclusion, bombe, angle-closure)". This type of change was assumed to result from migration of iris pigment epithelium into the trabecula. Although some more recent studies have shown that PAS is closely related to angle width and IOP [9,67,77,78], Barkan [76] also found that PAS was not uniquely present in narrow angle eyes. He also pointed out that the PAS foci in PACG cases differ from those in POAG cases in that they were found to rarely extend uniformly throughout the circumference, not limited to the Schlemm's zones, and only found in those portions of the angle in which other signs and symptoms exist to indicate that previous angle-closure had taken place. Obviously, according to our current understanding of pigment changes in ACA of different types of glaucoma, the same term of "trabecular pigment band" that Barkan used for PACG and POAG actually represents a totally different nature in terms of the pathogenesis and pathologic changes. Apart from mechanical obstruction to the trabecular meshwork by the peripheral iris, PAS may also indicate pathological changes in the functioning part of trabecular meshwork per se. One of the explanations that Barkan [76] proposed for inadequate effect of pharmacological miosis and iridectomy in opening up the drainage

angle was that PAS in PACG might be accompanied by the sclerosis and reduced permeability of the trabecular meshwork.

Although gonioscopy remains the current reference standard out of various assessment techniques for identifying narrow angle, it is a technique that requires considerable expertise, relies on subjective assessment in real time, involves contact with the cornea [79] and has substantial inter-observer variability [62] , which compromise its suitability as an initial screening test. So far, for such an examination technique that has been widely used in clinical practice for decades, its reproducibility has only been reported in a few studies of small sample sizes. The variability of results due to different illumination conditions and subjectivity is still a cause of concern when assessing reports on angle-closure based on gonioscopic findings. [62] Besides, it is difficult to verify gonioscopic findings reported in clinical and research settings, since so far it is still technically challenging to obtain good images of the anterior chamber angle (in terms of what ophthalmologists observed during gonioscopy) photographically [62].

1.3.3. Anterior segment imaging systems

Out of the numerous rapidly evolving imaging technologies in ophthalmology, several anterior segment imaging systems are particularly useful in revealing ACA-related anatomical structures. Apart from qualitative assessment by observing the images acquired, these techniques also provide objective quantitative measures of ACA and

ACA-related structures. These measures may help determine anatomical factors related to the risks for developing angle-closure.

1.3.3.1. Ultrasound Biomicroscopy

In early 1990s, ultrasound biomicroscopy was introduced as an innovative technique for imaging of the ocular anterior segment.[80,81] This imaging technique was developed based on the traditional ultrasound B-scan technique. The application of a high-frequency transducer brought compromised distance of tissue penetration (around 5 mm), but allows for a much clearer and detailed observation of the anterior segment owing to the increased resolution (lateral: 40 μm, axial: 20μm).

As one of the forerunners who firstly introduced UBM into the area of ophthalmic imaging, Pavlin and colleagues introduced quantitative analysis to the application of this technique and later developed a set of measurement methods to quantitatively reflect the anatomical structure of the ocular anterior segment. [81,82] These methods were represented by the following parameters, which were later widely used in the research area and also adopted in the quantitative analysis of images acquired using AS-OCT:

Angle Opening Distance (AOD):

A line is extended from a point 250 μm anterior to the scleral spur to the opposing iris,

being perpendicular to the plane of trabecular meshwork. AOD250 is defined as the length of this line. The definitions of AOD500 and AOD750 are quite similar to that of AOD250 except that the measurement was made at a point 500 μm or 750 μm anterior to the scleral spur.

Trabecular-iris Angle (TIA):

Starting from the apex of the angle recess, tangents to the iris and the angle are drawn through the point on the trabecular meshwork 500 μm anterior to the scleral spur and the perpendicular opposite point on the iris.

Trabecular-ciliary Process Distance (TCPD):

A line is drawn perpendicularly at the point on the trabecular meshwork 500 μm anterior to the scleral spur through the iris and to the ciliary process. The length of this line was termed TCPD.

Iris Thickness 1/2/3 (IT1/IT2/IT3):

A line is drawn perpendicularly at the point on the trabecular meshwork 500 μm anterior to the scleral spur through the iris. The thickness of iris measured along this line was termed IT1. The thickness of iris measured along a perpendicular line drawn at a point 2 mm from the iris root was termed IT2. The thickness of iris measured along a perpendicular line drawn at the thickest point of the iris near the pupil was termed IT3.

Scleral-iris Angle:

Scleral-iris angle was defined as the angle between the tangent line drawn along the scleral surface and the long axis of the iris.

Scleral-ciliary Angle:

Scleral-ciliary angle was defined as the angle between the tangent line drawn along the scleral surface and the long axis of the ciliary body.

Iris-zonule Distance:

Iris-zonule Distance was defined as the perpendicular distance between the posterior surface of the iris to the anterior zonules at a point that just clears the ciliary process.

Despite being a rather uncomfortable imaging technique which requires an immersion bath to be placed on the surface of the eye, the characteristics that singles UBM out from other anterior segment imaging techniques include the ability to acquire images through opaque media, penetration through the ciliary body, and less susceptibility to absorption by pigment in the iris. [83] The ability to visualise the ciliary body is important for understanding the anatomical features that determine the angle configuration. Apart from the above quantitative parameters involving the ciliary body, qualitative classification system based on reference standard UBM images [84] has also been introduced, covering various anatomical features related to the anterior chamber angle, such as: basal iris thickness, overall iris thickness, iris curvature, iris insertion, iris angulation, ciliary body position, and ciliary body size.

1.3.3.2. Anterior Segment Optical Coherence Tomography

Compared to UBM, the advantages of Anterior Segment Optical Coherence Tomography (AS-OCT) are that it is non-invasive, it is relatively less time-consuming, and it has comparatively higher image resolution with excellent visualisation of corneal and anterior chamber angle structures of both quadrants on the cross-sectional images. As a completely non-invasive imaging technique, AS-OCT provides in vivo cross-sectional images of tissue structures using low-coherence interferometry. [83] Although AS-OCT does not allow clear visualisation of the ciliary body and sometimes cannot clearly show the angle recess, important anatomic landmarks such as the scleral spur can be shown more distinctively in AS-OCT images.[85]

The physical principle underlying OCT is optical coherence. Basically, light beam generated from the interferometer is oriented onto the measurement target. Reflection from the measurement target is then combined with the reflection from the reference mirror for the calculation of dimensional size of the measurement target. OCT was introduced for medical imaging by Huang et al [86] in 1991. The application of OCT in the anterior segment of ocular structures was firstly demonstrated by Izatt and colleagues [87,88] in 1994 using an 830-nm wavelength light source. Trans-scleral OCT using 1310-nm wavelength light was then introduced by Hoerauf et al [89] in 2000. The scanning speed of early AS-OCT models was very slow. The acquisition time ranged

from 1 to 5 seconds per image, which made the system very sensitive to misalignment and artefacts from involuntary eye movements during the examination. Ideally, OCT instruments for real-time imaging should allow fast acquisition and processing of the scans. [83] In 2001, Radhakrishnan et al [83] reported an OCT system with increased scanning speed (8 frames per second) and a depth resolution of 8.1 μm, which was coupled to a hand held probe (which was later positioned at the slit-lamp in modified models) for the purpose of ophthalmic use. Theoretically, to maintain the required level of signal-to-noise ratio, the optical source power must be increased with the frame rate. In this new OCT system, a semiconductor optical amplifier light source operating at 1310-nm wavelength was employed. According to the theory that "absorption and scattering in most tissue constituents is a decreasing function of wavelength in the near infrared spectrum whereas absorption in water (the primary constituent of vitreous humour) increases sharply", as compared to 830-nm wavelength light, the 1310-nm wavelength light adopted in the AS-OCT also allows increased penetration into sclera and iris without causing damage to the retina. The availability of customized software [90] has made it possible to quantitatively analyse AS-OCT images and calculate parameters such as AOD, ARA, and iris thickness with high reproducibility [91].

1.3.3.3. Spectral-domain Optical Coherence Tomography

Compared to the conventional time-domain optical coherence tomography, spectral-domain optical coherence tomography (SD-OCT), also known as Fourier-domain

optical coherence tomography (FD-OCT), allows for both higher scanning speed and higher image resolution. The physical or working principles of SD-OCT is quite different from those of TD-OCT, it operates by collecting signals related to different wavelengths of light, and using Fourier transform algorithms to generate an image.[92] SD-OCT is a particular implementation of the above principles of FD-OCT. It collects all of the wavelengths of light at the same time using a spectrometer Although the value of SD-OCT has not been well established in the assessment of anterior chamber angle, SD-OCT differs from TD-OCT in its ability to clearly visualise the Schwalbe's line, Schlemm's canal and at least some proportions of the trabecular meshwork. However, with improved resolution, the depth and width of view provided by SD-OCT precludes complete imaging of the whole drainage angle up to the iris root, taking the risk of losing important information about angle configuration. [93,94]

1.3.3.4. Swept-source Optical Coherence Tomography

As a variation of SD-OCT, compared to TD-OCT, swept-source OCT has advantages similar to SD-OCT in terms of resolution and scanning speed. It differs from SD-OCT in having a 20-KHz scanning rate and high linearity in frequency sweeping, with the maximum resolution reaching 7.5 μm. This system enables acquisition of both 2-dimensional and 3-dimensional scans. The angle recess, which is often less clearly shown in SD-OCT imaging, can be sharply visualised in swept-source OCT images. Other important anatomical landmarks, such as scleral spur and trabecular meshwork,

can also be clearly shown in the 3-dimensinal images acquired by swept-source OCT.[95]

1.3.3.5. Scanning Peripheral Anterior Chamber Depth Analyser

The Scanning Peripheral Anterior Chamber Depth Analyser (SPAC) scans the anterior chamber from the optical axis to the temporal limbus and takes 21 consecutive images analogous to those produced by a slit-lamp. These measurements are automatically converted into numeric and categorical grades. Each eye was classified by the device on a numeric scale from 1 to 12, with 12 representing the deepest anterior ACD and 1 representing the shallowest. SPAC also reports categorical grades for risk of angle-closure: S (suspect angle-closure, if there were ≥ 4 points exceeding the 95% CI), P (potential angle-closure, ≥ 4 points exceeding the 72% CI) and no suffix (normal).[96-99]

Baskaran et al [100] compared the performance of the SPAC and the modified van Herick grading system in the assessment of angle-closure. SPAC correlated well with the modified van Herick grading system (categorical grade, r = 0.527; numerical grade, r = 0.542; P<0.0001) in qualitatively categorizing angle width. Using gonioscopy as the reference standard, the sensitivity and specificity of SPAC in identifying eyes with narrow angle were 84.9% and 73.1%, respectively. The corresponding sensitivity and specificity for modified van Herick grading system were 84.9% and 89.6%, respectively. Compared with gonioscopy that found 53 of 120 cases of narrow angles, the SPAC graded more eyes as having narrow angles (63/120) than the modified van Herick

system (52/120). Despite good correlation in between, SPAC appeared to overestimate the proportion of eyes with narrow angles compared to gonioscopy and the modified van Herick grading system.

Chang et al [79] reported that as compared to using SPAC alone, sequential testing using SPAC followed by AS-OCT could significantly improve the specificity of detecting narrow angles although this method might also result in slightly compromised sensitivity.

1.4. Risk Factors for Primary Angle-closure

In epidemiology, the term 'risk factors' is generally used to describe "any potential aetiological agent under study", and may sometimes also be used "in the more restricted sense of being a proven determinant of the disease" [101] . Risk factors can be conditions or characteristics that play important roles in the initiation or progression of disease, or response to therapies of a disease. In this literature review, the term 'risk factors' refers to factors that are associated with the onset and development of primary angle-closure. The roles that risk factors play in pathogenesis can be either protective against or contribute to the occurrence of the disease.[102] A clearer understanding of possible risk factors for PACG may help generate innovative prophylactic measures and treatment therapies. Despite increasingly active research into PACG over the past decade, the risk factors predisposing to development of primary angle-closure are still

poorly understood. PAC has been suggested to result from a combination of predisposing anatomy, environmental factors and their physiological responses [29].

1.4.1. Family history

Although so far no specific gene has been conclusively associated with PACG, previous studies on ocular dimensions among Inuit, Asian, and Caucasian populations suggested an important role of heredity in the aetiology of PACG [24].

The familial tendency to the development of PACG has been reported in many previous studies. In 1953, Tornquist [103] found the shallowness of the anterior chamber was influenced by heredity. Later in 1955, Kellerman and Posner[104] found 7% of eyes of relatives of “chronic simple glaucoma” patients had narrow angles, whereas 25% of the relatives of patients who had suffered attacks of acute angle-closure (AAC, previously described as “acute congestive glaucoma” in the literature) were found to have narrow angles. A much higher number of siblings with narrow angles was found in families with PACG patients than in those without.[105] In a study investigating ocular dimensions in the heredity of PACG, Tomlinson et al [106] reported shorter ACD, corneal diameter and axial length as well as greater lens thickness in siblings and children of PACG probands compared to normal controls. Of all the above ocular biometric measures, ACD showed the relatively largest deviation, suggesting that ACD might play a relatively more important role in reflecting the genetic influence on the aetiology

of PACG. By observing the iris colour, LACD, angular approach to the chamber recess, curvature of the peripheral iris, point of insertion of the iris onto the ciliary body, intensity of pigmentation of the posterior trabecular meshwork, and the nature of the iris process in 95 relatives of 10 people with acute, sub-acute or chronic primary angle-closure, Spaeth [64] classified the likelihood of developing acute angle-closure into 4 categories: angle occludable, probably occludable, probably not occludable, or not occludable. He found 20% of all relatives of those with a history of primary angle-closure have a probable risk of suffering from angle-closure, which is about 3 times more frequent than the risk of a large unselected population. A marked anterior convexity of the peripheral iris was observed 5 times more often in relatives of PACG patients than in controls. When looking at the similarity between the angles of PACG patients with their relatives who appeared to be clinically normal, greater similarity was found between relatives of closer relationship. Among the angle characteristics observed (including: iris profile, the radius of curvature of the iris, and the point of contact between the iris and the internal surface of the globe), anterior convexity of the peripheral iris seemed to have relatively the strongest correlation with angle configuration. This may support Spaeth's assertion that different characteristics of angle configuration have differing, independent inheritance patterns [61]. Epidemiologic studies among Greenland Eskimos also suggested a pronounced genetic influence upon the basic dimensional anatomy of the anterior chamber, which may probably constitute the genetic basis of PACG as well.[24,51] Alsbirk et al [107] reported a PACG prevalence of 12% in the siblings of PACG probands in the Greenland Eskimo population, comparing to the 3.5% PACG

prevalence in the overall local population. In particular, the PACG prevalence in female siblings was 17%, which was significantly higher than the 5.1% prevalence in females among the overall population. A relatively shallow chamber was found in 1st and 2nd degree relatives of Eskimo PACG patients, which was in close agreement with an earlier study in Caucasians [24,103]. A pronounced familial resemblance with respect to ACD and corneal diameter existed in the general Eskimo population.[24] In a population-based prevalence survey in China, Hu [36] also found a six-fold increased risk for subjects with family history of PACG.

It has been suggested that anatomical features of ocular anterior segments in individuals at high risk of angle-closure might be controlled by polygenic mechanisms.[7,108] The aggregated effects of multiple genes may result in similar characteristics as single major genes.[108]

1.4.2. Race

Racial background, presumably representing an individual's genetic makeup, has been recognised as a relatively imprecise term. Some categories of ethnicity do not necessarily represent genetic similarity. The quality of ethnicity data from different studies also varies widely since some studies collect information about assignment of ethnic groups by patients' self-report or self-description, whereas others rely on research staff attribution with or without standardised guidelines [102].

The tendency of a higher prevalence of PACG in certain ethnic groups has been widely reported from many studies. Lots of evidence has shown that PACG is much more prevalent among Greenland Eskimos and East Asian populations than in Caucasians and Blacks.[5,8,9,23,29-31,109-112] It was believed that the prevalence of PACG among Chinese populations is 5 to 10 times higher than among persons of other racial backgrounds.[38] Apart from relatively lower incidence, acute PACG in Blacks manifests as having fewer objective signs and subjective symptoms [43,113,114]. (See 2 for more details)

Many efforts have been made seeking for evidence of a difference in ocular anatomy between people of different ethnic backgrounds. Wang et al [115] recently compared variables in quantitative analysis of AS-OCT images of normal adult Caucasians and Chinese with open angles. Compared to Caucasians, Chinese subjects were found to have significantly smaller ACA and ACV (anterior chamber volume) than Caucasians. However, no significant difference was found when comparing ACA and ACV between American Chinese and southern/northern Chinese in mainland China. Interestingly, gender differences in ACA and ACV were only found in subjects of Chinese ethnicity. Female Chinese subjects were shown to have smaller ACA and ACV.

1.4.3. Demographics

Population-based studies have consistently documented higher prevalence of PACG and PAC suspects among women and older persons [8,77,116-118]. It is generally believed that women are affected by PACG more than 3 times as often as men[38]. In 1971, in the publication introducing his new grading system of angle configurations in gonioscopy, Spaeth reported the gonioscopic findings in 947 eyes of Caucasians aged 0.2 to 97 years [63]. He specifically looked at the changes in the gonioscopic appearance of the anterior chamber angle that occur with increasing age, and found a clear tendency of ACD to become shallower with increasing age. Among subjects of all age groups, only 1.1% of all eyes had very narrow angles in which the iris was found to be in close contact with the trabecular meshwork. However, this proportion was up to 10% among those aged 88 to 92 years; 5% among subjects aged 83 to 87 years; 4% in the 78-to-82 age group; and 0% among subjects younger than 78 years. Spaeth's findings were in concordance with the report from Van Herick, Shaffer and Schwartz, who found narrower angles occurred with far greater frequency in the elderly, and wider angles in the young [48]. In a study comparing configurations of the anterior chamber angles among people of European, African, and east Asian descent using quantitative biometric gonioscopy [119], Congdon and colleagues [120] found although mean angle width measured by biometric gonioscopy did not generally differ by race, the mean angle width for younger Chinese is above that of black and white people, whereas the mean angle width of older Chinese was relatively narrower. However, the strength of this study was limited by the small sample size. Similar to the findings of many other

studies, older age and female sex were both found to be associated with narrower angle measured by biometric gonioscopy. The prevalence of PACG exponentially increases with age after 40 years of age.[121] Chinese females showed a more dramatic drop in angle width with increasing age than Chinese males, with the narrowest angles found in older Chinese women. However, such sex differences were not significant for blacks and whites. Some researchers believe the narrower angles among women might be associated with a smaller overall ocular and general body size [122].

Similar findings also have been reported in studies of the incidence of acute angle-closure attacks. In an island-wide AAC incidence study in Singapore, Seah et al [123] reported remarkably higher incidence of AAC in females than in males, which was a specific finding among Chinese Singaporeans. The relative risk for the incidence of AAC in women compared with men was 2.4 (95%CI: 1.8-3.5). Highly significant difference in AAC incidence was found between the age groups 30 to 59 years and 60 years and older, with the relative risk in the latter group being 9.1 (95%CI: 6.7-12.3). Later in a report on rates of hospital admissions for PACG, Wong et al [124] reported an age adjusted rate of hospital admissions in women twice that of men, with the higher rates seen in all three ethnic groups (Chinese, Malays, Indians) in Singapore.

One of the most likely explanations for an increasing prevalence of PACG in older persons is the change in lens thickness with ageing [24,125,126]. The thickening of the lens leads to crowding of the anterior segment and the zonules that become more lax with

increasing age can result in the anterior displacement of the iris-lens diaphragm.[127] Previous studies also have reported a tendency of more pronounced age-related change in ocular biometrics in females than in males.[24,128] Eyes of Asian females at high risk of developing angle-closure were found to have significantly shorter axial length and steeper corneal curvatures compared to those of their male counterparts in the same study population.[21] Using UBM, Scheimpflug photography and gonioscopy, Friedman et al[127] gave further evidence that the anterior chamber angle is narrower in older individuals and women. Perhaps it is more appropriate to consider both age and sex as surrogates for some anatomical or physiological features, some genetic characteristics, and even possibly some socioeconomic factors affecting the access to health care facilities. Age is also a factor relevant to the length of time that an individual is exposed to other risk factors for the onset or development of the disease.[102]

1.4.4. Socioeconomics

Socioeconomic status, and specifically educational attainment and housing, reflect different access to health care services, exposure to environmental factors, health-related lifestyle, and near vision workload. Socioeconomic conditions can also affect patients' understanding about the disease, compliance with treatment, and the affordability for the cost of treatment. [129,130] In a recent study in Singapore, Friedman et al [54] compared the education and housing conditions between individuals who suffered from monocular AAC and normal controls. The proportion of individuals with

a secondary school education or higher was 20.4% in the AAC group, compared to 35.7% in normal controls selected from the same populations. Similarly, study subjects in the AAC group were also shown to live in housing of generally lower quality than the controls. These findings about a possible relationship between socioeconomic factors and angle-closure were later confirmed by Xu [129] and Yip [130] who identified education attainment as an independent protective factor for PACG. In the population-based Beijing Eye Study, Xu et al [129] found an association between higher level of education and lower prevalence of PACG using both univariate and multivariate models. In Yip's analysis based on data from a prevalence survey in Mongolians aged 50 years or older, individuals with no formal education were found to be approximately 7 times more likely to develop PACG compared to those with more than 8 years of formal school education. Housing condition has been regarded as a comprehensive measure of household/individual socioeconomic status, access to services and environmental conditions for a given area. The association between housing and PACG may reflect differences in access to medical care services, which may in turn influence the prevalence and prognosis of certain diseases. Similarly, different education attainment can also reflect different access to resources, different living style and exposure to different environments. Yip and colleagues[130] proposed some possible explanations for the association between higher education level and relatively lower risk for PACG, although no conclusive evidence could be generated from their data. Having more years at school was at first taken as a surrogate for more near work load, which might increase stimulus for longer axial length (causing axial myopia) and thus result in

reduced risk for PACG. However, this assumption was not proved by multivariate analysis which showed the effect of education on PACG was independent of axial length. Another explanation might be the different severity of cataract in people with different socioeconomic status. A bulky and thick lens can aggravate the crowding of the drainage angle. People with lower education attainment were found to have a tendency of suffering cataract of higher nuclear, cortical and posterior subcapsular opacity, possibly due to different access to cataract surgery service. [130]

1.4.5. Ocular Biometrics

A shallower anterior chamber has been more and more closely associated with angle-closure in research about PACG, and is even widely regarded as the leading anatomical risk factor for primary angle-closure [5]. Among Greenland Eskimos, shallow anterior chambers were found to be associated with a pronounced morbidity of PACG. Alsbirk [131] found all PACG patients identified in his study belonged to the lower half of the ACD distribution. If one arbitrarily draws a cut-off line in ACD values, approximately 18% of males and 24% of females with ACD below 2.0 mm had PACG. The mean ACD in both male and female PACG patients was 1.76 mm, comparing to the population level of 2.43 mm in males and 2.29 mm in females respectively. Meanwhile, they also found that the sex and ethnic differences in PACG prevalence corresponded remarkably well with the difference in ACD distributions. [131] The range of ACD below 2.10 mm using Zhao and Hu's proposed cut-off value for the Chinese population would

include more than 88% of PACG eyes. [36,132]

Apart from ACD, several other ocular biometric characteristics have also been reported to be possibly associated with risks for developing angle-closure. Lowe identified PACG as a disease occurring in undersized eyes having crowded anterior segment that may be accompanied by normal or enlarged crystalline lens, smaller radius of corneal curvature, shortened axial length [133]. This was later confirmed by Alsbirk et al[24], who found in Greenland Eskimos that eyes with PACG are characterised by smaller axial length, flatter corneas, shallower anterior chambers and thicker lens. In purpose of determining predisposing factors for acute angle-closure, Friedman et al [54] compared ocular biometry of the fellow eyes of individuals who suffered from unilateral AAC, which are at especially high risk of developing AAC if left untreated [55-57], with eyes of population-based control subjects in a Singaporean Chinese population using ultrasound biomicroscopy and Scheimpflug photography. Compared to normal controls and after adjusting for age and sex, the fellow eyes in unilateral AAC cases were shown to have significantly shorter axial lengths, shallower anterior chamber depths, thicker lenses, and steeper radii of corneal curvature. These outcomes are in accordance with the findings by Gazzard et al [21] in another study that compared eyes at risk of angle-closure with normal controls.

By quantitative analysis of images acquired using AS-OCT, several novel anatomical factors were reported as potential risk factors for angle-closure. Nongpiur et al [134]

reported the association between smaller anterior chamber width (ACW, defined as the horizontal scleral spur-to-spur distance in AS-OCT images) and individuals of older age, Chinese ethnicity, and narrow anterior chamber angle. The same group also reported significantly smaller anterior chamber area (ACA, defined as the cross-sectional area bounded by the corneal endothelium, the anterior iris surface and the anterior surface of the lens in the pupillary area in AS-OCT images) and anterior chamber volume (ACV, calculated by rotating the ACA 360° around a vertical axis through the mid-point of the ACA in the AS-OCT images) in narrow angle eyes. The association of ACA and ACV with narrow angle configuration was stronger among individuals of female gender and Chinese ethnicity [135].

In the multifactorial pathogenic mechanisms of PACG, ocular biometric parameters might have interactions with other factors while playing an important role in the pathogenesis of angle-closure. Several factors such as age, sex, refractive error and body stature all have been associated with central ACD [136]. Extensive family studies in Eskimos showed a high degree of resemblance between first-degree relatives in ACD measured by optical pachymetry. About 70% of age- and sex-independent ACD variations seemed to be genetically determined.[107] Comparing ACD of the background Eskimo population in Greenland with the immigrant Eskimo population in Copenhagen, Alsbirk et al [51] found a significantly higher ACD level in the immigrant sample than in the background population (2.48±0.32 mm vs. 2.29±0.33 mm, t=4.7, P<0.001). This result suggests that environmental factors have influenced ACD, although it is difficult

to find out exactly which factors are playing relatively more important roles. The influence from ethnicity in the pathogenesis of PACG is also confounded by ACD. Congdon [7] compared the population distributions of ocular parameters reported by previous studies and summarised that ethnic groups at greater risk for PACG have smaller and more crowded eyes with shallower anterior chambers. However, he also pointed out that the racial difference in the prevalence of PACG cannot be fully explained by the above anatomic risk factors although biometric parameters such as anterior chamber depth does differ among different racial groups [128,137]. Similarly, based on a cross-sectional study in Singapore, Lavanya and colleagues [138] also suggested that short axial length and shallower ACD cannot fully explain the relatively high prevalence of angle-closure in females and individuals of Chinese ethnicity. In other words, the predominantly higher prevalence of angle-closure in certain areas of the world does not completely result from a much higher proportion of small eyes in the population of those areas. As Quigley et al [38] have speculated, a more reasonable explanation might be that small eyes among the Chinese are more likely to develop PACG than small eyes among other groups, with contribution from other predisposing factors.

1.4.6. Anthropometry

The assumption that adult anthropometry (such as height, body weight, and body mass index) might be associated with angle configuration was initially generated from the

widely reported correlation between ocular biometric factors and refractive status and the risks for developing primary angle-closure.[139-143] Wong et al [136] found that adult height is independently related to ocular dimensions, but does not appear to influence refraction, which might be explained by a balance between ocular dimensions and the refracting power of different components in the ocular refractive system during the emmetropization of human eyes. On the contrary, in the same study, weight was found to be independently related to refractive status without significant association with ocular dimension. In more recent population-based studies among Chinese adults, Xu and colleagues [144,145] found a shallow anterior chamber and a narrow anterior chamber angle are associated with short body stature. Shallow peripheral anterior chamber (measured by limbal ACD) was also found to be associated with shorter heights, whereas no significant correlation between limbal ACD and weight or BMI was found.

1.4.7. Climatic and psychological factors

By analysing the association of genetic and environmental factors with ocular anatomical features in Eskimos, Alsbirk and colleagues[24] proposed that genetic adaptation to cold environments might play a role in the relatively high incidence of PACG among this specific arctic population. The highly vascular ciliary body and iris was once described by researchers as the 'heating elements' of the ocular anterior segment including cornea [24], which might form the physiological basis for the adaptation of the ocular anatomy of Eskimos to cold environments [146]. The authors

proposed an assumption that the shallow ACD among the Greenland Eskimos might result from a thermoregulatory adaptation to the cold environment. In eyes with shallower anterior chamber, the vascularized and warm iris tissue is positioned closer to the cornea, which might help prevent potentially blinding corneal freezing.[24] A shallow anterior chamber can bring the iris closer to the cornea, which may reduce the risk of corneal damage from freezing weather. The natural selection against deep anterior chamber and large cornea may have been an active force through the several thousand years of arctic life, which may represent a genetic adaptation to arctic environments. In an epidemiological study in Israel on the incidence of AAC, David et al [147] found a statistically significant preponderance of acute angle-closure attacks during summer and winter. The same or slightly different association between seasons and acute angle closure have also been reported elsewhere [123].

Emotional status has also been listed as one of the risk factors for angle-closure. In early case reports on emotion-related glaucoma, emotional precipitates were associated with the development of acute attacks of angle-closure. [148] Emotionally-charged life events that bring about emotional stress, unpleasant experience or excitement have also been reported to be possible predisposing factors for AAC attacks.[149] Although the mechanisms of the association between angle-closure and emotional status are still not well understood, increased risk for relative pupillary block due to the possible pupillary dilation caused by stress might be one of the likely explanations.[108]

1.5. Mechanisms for iridotrabecular apposition and synechial angle-closure

1.5.1. Pupil block mechanism

Pupil block is believed to be the major mechanism ascribed to primary angle-closure. According to Tiedeman's theory about the physical factors affecting iris contour [150], which was later supported by Jin et al [151] using Scheimpflug anterior segment photography, the contour of iris is determined by a combined effect from the pupil dilator muscle fibres, the pupil sphincter muscle fibres, the force acting to hold the iris root, and the hydrostatic pressures from the posterior and anterior chamber [12]. The tiny space between the iris and lens, described by Silver and Quigley [152] as "the iris-lens channel", creates the main resistance to the aqueous flow from the posterior chamber to the anterior chamber. In normal conditions, the lens is assumed to be not in touch with the iris. In pupil block, the pressure difference between posterior and anterior chamber is created by the resistance to aqueous flow from back to front at the pupillary margin. This pressure gradient between the posterior and anterior chamber then results in the anterior bowing of the iris (i.e. iris bombé), which can possibly result in appositional iridotrabecular contact. When the anterior lens surface is positioned more anteriorly than the iris root, and when the pupil is in the mid-dilated position, the resistance at the iris-lens channel may increase dramatically and even completely obstruct the aqueous flow from the posterior chamber to the anterior chamber. This

may cause acute and remarkable IOP elevation.

The risk of pupil block is particularly high in eyes of relatively small dimensions. In theory, the aqueous flow in undersized eyes with predisposing anatomical features of angle-closure may not be as continuous as in eyes of normal or large dimension [13]. It is assumed that in eyes at risk of angle-closure, the iris tends to remain in the same plane as its insertion spot, leading to a greater area of contact between the iris and the lens and may possibly result in relative pupillary block. As indicated by the name, relatively pupillary block forms a relative barrier for the aqueous humour to pass from the posterior chamber through to the anterior chamber. To overcome this relative barrier and ensure a continuous aqueous flow, the pressure in the posterior chamber has to be adequately increased. However, this may lead to the forward bowing of the peripheral iris, which will narrow down the drainage angle furthermore and finally occlude the trabecular meshwork. Quigley [38] pointed out that relative pupillary block is actually very commonly seen in phakic eyes. However, greatly increased resistance in the iris-lens channel and remarkably anterior bowing of the iris that will finally lead to appositional angle-closure [152] will only occur in eyes with more anteriorly positioned lens or other predisposing factors [38].

1.5.2. Non-pupil block mechanism

Other non-pupil block mechanisms have also been suggested to be responsible for

the pathogenesis of PACG, which involve configurations of the peripheral iris, damage to the trabecular meshwork, anatomical features of the ciliary body and suprachoroidal space, thickness and position of the lens, and movement of iris-lens diaphragm.[12,153,154] Although as a first-line treatment for PAC and PACG, laser peripheral iridotomy (LPI) has been proved to be able to open up the pre-treatment narrow or closed angle in the majority of cases, some previous studies have also reported various proportion of cases in which the angle remained narrow after LPI [153,155,156].

1.5.3. Mechanisms associated with the Iris and Ciliary Body

Evidence from UBM imaging has shown that the anteriorly rotated ciliary body as well as bulky peripheral iris can play important roles in keeping angles narrow or even closed with the existence of a patent iridotomy. Although the iris profile flattens after an LPI, the structural support from the ciliary body may keep the peripheral iris at an adequately anterior position so as to form a potentially occludable angle. [153]

Apart from static anatomical features, the role of dynamic behaviours of the iris has recently aroused wide interest among PACG researchers. Friedman et al[54] compared the dynamic change of angle width under different illuminations conditions using UBM and Scheimpflug camera in fellow eyes of unilateral AAC cases and normal controls. They found although the anterior chamber angle narrowed down in both groups when the illumination changed from light to dark, the angle opening distance (AOD, 500 μm

and 750 μm from the scleral spur) in UBM scans decreased more than twice as much in the fellow eyes than in normal controls. In this study, dynamic changes of angle width before and after pharmacologic miosis by topical pilocarpine were also observed. The AOD (500 μm and 750 μm from the scleral spur) increased around 50% less in the fellow eyes of unilateral AAC cases as compared to normal controls 30 minutes after topically applying 4% pilocarpine. In Scheimpflug photography, comparing to 1.8º in controls, the angle width increased by 1.2º in the fellow eyes 30 minutes after administering 4% pilocarpine eyedrops. These observations of dynamic response to changes in illumination and medical treatment with pilocarpine have indicated possible association between differential reactions to these stimuli and acute attacks of primary angle-closure. [54] Quigley et al [157] compared the cross-sectional iris area measured in AS-OCT images before and after physiological and pharmacological mydriasis. The iris was found to lose almost half of its volume when the pupil diameter changed from 3 mm to 7 mm. However, compared to individuals diagnosed as having POAG or identified as POAG suspects, those with angle-closure had less decrease in cross-sectional iris area per millimetre pupil enlargement. These findings suggested that smaller change in iris cross-sectional area with physiologic pupil dilation (with the illumination changed from light to dark) might be a risk factor for angle-closure and might also partly explain the well-known association between dim light condition and the incidence of acute attacks of angle-closure. The authors speculated that the rapid (completed within 5 seconds) and prominent decrease in iris volume may be associated with a rapid exit of extracellular fluid from the iris stroma into the anterior

chamber, a condition that possibly differs between eyes with and without narrow angles. Apart from the change in iris volume and thickness, one study comparing subjects of Chinese ethnicity with PAC/PACG and with open angles found an independent association between the pupil dynamics (a potential surrogate marker of iris dynamic behaviours) and angle configuration. After adjusting for age, anterior chamber width (ACW, measured in AS-OCT images), ACD, iris thickness and vertical cup-to-disc ratio, eyes with closed angles were shown to have slower speed of pupil constriction in response to dark-to-light change in illumination. Furthermore, the authors also found an association between pupil diameter in dark and the speed of pupil constriction. The pupil tended to constrict faster in persons with larger pupil diameter. [158] This association might be related to different amount of illumination on the retina in eyes of different pupil diameters.[159]

Using a customised image-processing software, Aptel and Denis [160] calculated iris volume from cross-sectional iris area in AS-OCT images of 8 radial sections. They compared the change of iris volume caused by pharmacologic dilation between the fellow eyes of 30 patients with a unilateral episode of primary AAC and eyes of 30 age- and gender-matched healthy controls with open angles. While the mean iris volume did not differ significantly before dilation, it increased significantly in the fellow eyes of unilateral AAC cases and decreased significantly in the control eyes with open angles after pharmacologic dilation created both by instilling 1% tropicamide alone and by instilling 10% phenylephrine alone. The angle width also decreased in the fellow eyes

after dilation while remaining basically unchanged in the controls. In the univariate regression model for change in iris volume, fellow eyes of unilateral AAC patients, brown eyes and large pupil diameter were found to be significant predictors of higher increase in iris volume after pharmacologic dilation. Partly in agreement with Quigley's assumption [157], Aptel et al also speculate that the different patterns of change of iris volume in response to pharmacologic dilation between eyes with and without narrow angle configuration might indicate some differences in dynamic behaviours of the iris stroma, especially the extracellular fluid transfer and/or vascular tonus change. These study outcomes may contribute as evidence for the role of dynamic iris behaviour as one of the mechanisms involved in the development of angle-closure in dilated and partly dilated eyes.

1.5.4. Lens-related mechanisms

Thick and anteriorly positioned lenses have been recognised as lens-related risk factors for angle-closure. The thickness and position of the lens has been suggested to play an important role in the pathogenesis of PAC. There has been evidence suggesting that a generally thicker lens with a relatively more bulky part anterior to the scleral spur may create more resistance to aqueous flow at the iridolenticular contact area, aggravating pupil block, anterior iris bowing, and angle crowding. [161] Eyes with closed angles were found to have significantly higher lens vault (LV, defined as the perpendicular distance between the anterior pole of the crystalline lens and a

horizontal line joining the 2 scleral spurs) and lens thickness (LT) comparing to normal controls, whereas no difference was found in lens position (LP, defined as ACD + 1/2 LT) and relative lens position (RLP, defined as LP/axial length) between eyes of closed and open angles.[162] In another study involving 1465 participants aged 50 years and older (of which 315 had gonioscopically narrow angles), Tan and colleagues [163] found eyes with narrow angles had greater lens vault compared to those with open angles. Females were found to have significantly greater lens vault compared to males. In analysis using multivariate regression models, the lens vault was identified as a risk factor for angle-closure independent of lens thickness and lens position. [162]

1.5.5. Mechanisms associated with suprachoroidal/uveal effusion

The choroid is a highly vascular structure with high ratios of blood flow to tissue volume. The suprachoroidal space is a potential space sitting between the choroid and the sclera. Although the physiologic mechanisms which are responsible for producing and eliminating serous fluid from the suprachoroidal space have not been fully understood, the volume and thickness is supposed to be possibly regulated by the pressure within the choroid vessels, colloid osmotic pressure of the choroidal extracellular space, and IOP. [38] Due to the elasticity of the choroid, the loss of fluid across the sclera and emissary channels, and the fluid absorption into choroidal vessels from colloid osmotic pressure differences, the pressure in the suprachoroidal space is 2 mm Hg lower relative to the pressure in the vitreous cavity [164]. This pressure difference produces a

natural tendency for the choroid to expand inward. Previous research has provided some evidence to show that choroidal expansion might be associated with form deprivation and acute elevation of episcleral and orbital pressure [165-167]. Due to the fact that the scleral surface decreases by the square of the ocular radius, which might compromise the ability of scleral conductivity, choroidal expansion can be especially more long-lasting in eyes of relatively smaller dimensions [38].

Choroidal expansion, which has been detected in some AAC eyes [168], can be caused by many factors including inflammations, infections, suprachoroidal haemorrhage, high vortex vein pressure, small ocular dimension, tumours, pharmacological reaction, and arteriovenous malformations [54,169-175]. It is clinically apparent and also confirmed by anterior imaging that forward movement of the iris-lens diaphragm is characteristic of PACG-affected eyes, both intraoperatively and in a greater tendency to flat anterior chamber after filtration surgery. [54] In a review discussing possible mechanisms of PAC and malignant glaucoma, Quigley and colleagues [38] proposed a hypothesis that expansion of the choroid could transmit force to the anterior structures, pushing the iris-lens diaphragm forward. An expansion of only 20% in Choroidal volume would occupy a volume approximately equal to the entire anterior chamber volume in an eye with the typical anatomy for PACG.

A previous study comparing deepening of ACD after LPI [21] have found that in patients with unilateral acute angle-closure, ACD deepened significantly more in the affected

eye than in the fellow eyes 4 months after LPI. A hypothesis was that the greater difference in ACD before and after LPI in the affected eyes was associated with the anterior movement of the lens during the acute attack, which might be caused by the expansion of the choroid. And in fact, increase in choroidal volume does have the ability to cause remarkable anterior movement of the lens. [38]

1.6. Treatment of Primary Angle-closure

The main purpose of treatment for PAC is to open up the drainage angle, eliminate the obstruction of the outflow pathway and lower IOP with medical or surgical interventions.[176]

1.6.1. Laser Treatment

1.6.2. Laser Peripheral Iridotomy

LPI has been recommended in the American Academy of Ophthalmology's (AAO) Preferred Practice Patterns guideline as the preferred initial treatment for PAC and PACG. PACS, however, was not particularly recommended as an absolute indication for iridotomy. Instead, for individuals with iridotrabecular contact, it is recommended in the AAO preferred practice patterns that "iridotomy may be considered to reduce the risk of developing angle-closure. Alternatively, patients with irido-trabecular contact

may be followed for development of IOP elevation, evidence of progressive narrowing, or synechial angle-closure, since iridotomy can be associated with bothersome postoperative glare/diplopia".[177-179] Compared to surgical iridectomy, LPI is less expensive, less invasive and less time-consuming. Theoretically, LPI can create an opening in the peripheral iris to bypass aqueous humour for the purpose of eliminating pressure difference between the anterior and posterior chamber in relative pupillary block. Recent data from the UK Department of Health's Hospital Episode Statistics (HES) also shows that the increase in the total number of LPI and phacoemulsification procedures performed per year has resulted in a remarkable decrease in the incidence of acute angle-closure in the United Kingdom.[180]

When the argon laser was first introduced, it was used in LPI. Argon laser mechanism of action is through photocoagulation of tissues, resulting in shrinking and charring of tissue. However, one of the drawbacks of the photocoagulation effects was subsequent closure of iridotomy after the procedure. Early case series reported a high subsequent closure rate of up to 30%. [181,182] Later in the 1980s, Nd:YAG laser was reported to be able to achieve a higher rate of single treatment success and lower risk of subsequent closure.

The evaluation of efficacy of the treatment for glaucoma usually involves the assessment of change in angle configuration, long-term control of IOP, progression of PAS, and changes in visual fields defects. Recent studies have shown that LPI might

help slow down or even stop progression of the disease and protect visual function if applied in the early stage of PACG. However, for eyes with extensive PAS as well as established glaucomatous optic neuropathy and visual field defect, LPI was found to be unable to produce satisfactory long-term outcomes. In a study among Mongolians [155], LPI was found to be effective in widening the ACA and bringing the elevated IOP back to the normal level in eyes identified to be PAC. Treatment failed in 47% of eyes diagnosed to be PACG. In another study conducted in Singapore, after treated by LPI, nearly 90% of PACG cases needed additional medical treatment for IOP control, while more than 45% eventually needed surgical intervention. [183] Rosman et al [184] studied the long-term clinical course of North American chronic angle-closure glaucoma (CACG) patients with optic disc damage and visual field loss in the presence of an angle closed at least partially by PAS and generated similar results. Similar to the aforementioned findings in Mongolia, most of the eyes with established PACG needed further medical treatment for IOP control after LPI.

Although LPI has been proved to be effective in preventing acute attacks in the fellow eyes of unilateral APAC patients [185,186], LPI alone does not appear to be a wholly effective treatment for eyes that suffer from acute angle-closure. Choong and colleagues [187] have showed that 56% of the patients required further treatment on follow-up after receiving LPI, with 21% on topical anti-glaucoma medication alone and 35% being in need of further surgical intervention after LPI. Another study reported a rate of 58.1% in APAC cases that require further treatment due to uncontrolled IOP

despite a patent LPI.[188] Although the role of LPI in the treatment of the chronic form of PACG still remains disputable, using gonioscopically open angle as the criteria for success, LPI was shown to be capable of opening up angles in over 70% of eyes having chronic ACG, with similar success rate achieved in eyes with chronic appositional angle-closure and chronic synechiael angle-closure.[156]

Theoretically, LPI should be effective in PAC cases that are developed primarily based on the pupil block mechanism. This procedure eliminates pupil block and equalizes the pressures in the posterior and anterior chambers.[74] However, research on the pathogenesis of angle-closure has suggested that the coexistence of pupil block and non-pupil block factors as mixed mechanism is quite commonly seen in East Asians.[189,190] A recent population-based study in southern China has shown that the angle remained narrow and occludable in 20% of PACS eyes after LPI. Although limited by small sample size and short follow-up period, several recent studies have shed light on the possible mechanisms leading to inconsistent outcomes after LPI. In a prospective study comparing anterior chamber parameters before and after LPI using quantitative analysis of AS-OCT images, Huang et al found that eyes of older individuals with smaller iris area, steeper iris curvature are more likely to attain greater anterior angle opening after LPI. Identification of age as an independent predicting factor for angle widening may indicate different mechanisms of angle-closure among older and younger individuals. In studies on mixed samples comprising eyes with PACS, PAC and PACG, the outcome of LPI was found to be unrelated with the different

types of angle-closure conditions. No statistically significant difference was found in the degree of angle widening between PACS, PAC and PACG after LPI.[191,192]

Previously reported complications of LPI include transient IOP elevation, damage to the corneal endothelium and corneal opacities in the corresponding areas, iris bleeding, and increased severity or faster progression of lens opacification due to localized damage.[193] Posterior-segment complications of LPI are rarely seen.[194] Anderson[195] reported a case of stage1 macular hole that developed following LPI using sequential 532-nm green diode laser and Nd:YAG laser. The onset of the macular hole was reportedly followed by complete posterior vitreous detachment and resolution of the macular hole with significant improvement in visual acuity. This was accompanied by resolution of the central scotoma. The pathogenic mechanism was assumed to be related to concussive shock waves and thermal effects produced by laser through the anterior hyaloid face to the vitreous body, which may possibly cause a peri-foveal vitreous detachment with subsequent foveolar traction and finally led to the formation of macular hole. There has also been a published report describing immediate loss of vision caused by inadvertent foveal photocoagulation[196].

1.6.3. Laser peripheral iridoplasty

In contrast to LPI, which widens the anterior chamber angle by eliminating pupillary block and flattening the peripheral iris, laser peripheral iridoplasty exerts its therapeutic

actions by shrinking and pulling the peripheral iris tissue away from the trabecular meshwork. In the current standard treatment pattern, iridoplasty is mainly recommended as an option for patients with persistent appositional angle-closure after LPI.[176] Despite this recommendation, iridoplasty has been considered by some clinicians as one of the first-line treatment methods for acute attacks of angle-closure. In a cases series of 10 patient with AAC and IOP elevation above 40 mm Hg, Lam et al[197] treated AAC with immediate iridoplasty and observed a dramatic decrease of IOP (from nearly 60 mm Hg before iridoplasty to 16 mm Hg one hour after iridoplasty). So far, very limited evidence is available on the application of laser peripheral iridoplasty in cases with chronic asymptomatic form of angle-closure. In a randomised clinical trial, Sun and colleagues[198] found no benefit in using laser peripheral iridoplasty as an adjunct to LPI for IOP reduction in terms of number of medications used, the need for further surgical intervention or visual function. However, a significant reduction in the range of PAS was found in the LPI plus iridoplasty group. In a small non-controlled prospective study [199], to minimise the chance of angle re-closure, diode laser peripheral iridoplasty was used on the 4th day following gonio-synechialysis over a 180-degree circumference of the angle in patients with chronic PACG and total synechial angle-closure. Anatomical success was achieved in 80% of patients. In another case series study, Ritch et al [200] retrospectively reviewed the outcomes over a mean follow-up period up to 78.9 months after laser peripheral iridoplasty in 23 eyes of 14 patients. The satisfactory long term success rate also showed evidence for the safety and efficacy of this procedure.

Laser iridoplasty performed with an argon or diode laser has been advocated for the management of PACG [201,202]. The typical settings for argon laser in iridoplasty comprise a 500 μm spot size, a duration of 0.5 seconds, and a starting laser energy of 50 to 200 mW [176]. In this procedure, laser burns of long duration, low power, and large spot size, are applied to contract the stroma of the peripheral iris generating physical traction for the purpose of pulling open the drainage angle. It has been suggested in ocular pathologic research that after the initial short-term angle opening possibly produced by heat shrinkage of collagen in response to the argon laser energy, long-term effect of the procedure may be maintained by the contraction of the fibroblastic membrane. [203] Iridoplasty has been shown to effectively reduce IOP in PACG cases with IOP poorly controlled by medical therapy [201]. Although results of some recent studies suggested that laser peripheral iridoplasty might be applied as an alternative to conventional medical therapy in treating APAC and was shown to be effective in improving corneal transparency by controlling IOP [197,204,205] , so far there is no conclusive evidence available in regard to the optimal timing of application and the long-term efficacy of laser peripheral iridoplasty for the treatment of PACG. In clinical practice, for the treatment of APAC, LPI still has to be performed after initial laser peripheral iridoplasty since there are still very limited data available about the long-term efficacy and safety of this procedure [12].

1.6.4. Surgical Treatment

The main goals for surgical intervention in the treatment of PACG include: to rapidly control IOP, to prevent progression to chronic angle-closure, and to treat chronic PAC eyes with uncontrollable IOP. [206] Although evidence shows that most individuals with IOP outside the typical range in a population do not eventually develop glaucoma [207], satisfactory control of IOP can slow down the progression of glaucoma [121]. Many surgical options are available for the treatment of PACG, including surgical iridectomy, filtering surgery, lens extraction, angle-widening procedures, cyclodestructive procedures and various combinative procedures [12,208-216]. So far, no consensus has been reached on the optimal or first-line choice of surgical procedures for PACG.

Trabeculectomy is the most widely used surgical treatment for glaucoma. The main purpose of performing trabeculectomy is to lower the IOP. The indication of performing trabeculectomy is limited to cases in which the remarkably elevated IOP cannot be controlled by iridotomy or iridoplasty in the presence of extensive PAS. If used for the treatment of chronic PACG, caution should be taken to prevent post-operative flat anterior chamber and malignant glaucoma. [206]

A bulky and anteriorly positioned lens with a steep anterior lens surface can aggravate relative pupil block and lead to angle-closure in eyes with other predisposing anatomic features.[217] The role of lens in the pathogenic mechanism of angle-closure has aroused wide interest in adopting lens extraction as the surgical intervention to widen the

drainage angle, reduce the range of angle-closure, and eliminate the risk for relative pupil block. In the treatment of chronic PAC, lens extraction procedures such as extracapsular cataract extraction (ECCE) and phacoemulsification have been proven to be effective in IOP control. [213,218] Improved surgical outcomes have been reported in cases undergoing combined phacoemulsification and trabeculectomy [219], which is possibly associated with the reduced incision size in the combined procedure. The replacement of the bulky natural crystal lens with a thin IOL can also possibly reduce the risk of flat anterior chamber following trabeculectomy. [206]

1.6.5. Medical treatment

Unlike the treatment of POAG, medical treatment is not regarded as an appropriate first-line option for the treatment of PAC or PACG. However, in cases where laser or surgical procedures cannot produce a satisfactory outcome, long-term use of topical medications may still be necessary. A recent meta-analysis [220] involving 1090 chronic PACG patients from randomised clinical trials suggests that prostaglandin, currently recognised as the most potent category of ocular hypotensive medications, are most effective for reducing IOP by monotherapy in chronic PACG patients. The greatest IOP reduction with topical medication was achieved by latanoprost, followed by travoprost, bimatoprost, and timolol. Most of the currently available evidences about medical treatment for glaucoma focus on POAG and ocular hypertension (OHT). Very limited data are available for clinicians to generate “optimal” medical treatment strategies for

PACG, topical beta-adrenergic receptor antagonists or cholinergic agonists are sometimes used empirically as a first-line medication [12] to reduce IOP in such patients. Aung et al [221] conducted a randomised double-masked prospective study and compared the efficacy of topical latanoprost (latanoprost group: placebo in the morning and latanoprost 0.005%) and timolol (timolol group: timolol 0.5% twice daily) in eyes with PACG. Patients were randomised to one of two parallel treatment groups, mean IOP reduction in latanoprost group was 8.8 ± 1.1 mm Hg from a mean baseline IOP of 25.7 ± 0.9 mm Hg, whereas the timolol group only achieved a significantly lower reduction: 5.7 ± 0.9 mm Hg from a mean baseline IOP of 25.2 ± 1.1 mm Hg. Hung and colleagues[222] prospectively examined the treatment efficacy of latanoprost 0.005% once as adjunctive topical treatment for post-LPI PACG patients with IOP poorly controlled by beta-blockers and pilocarpine. The IOP decreased by about 21% during the first 3 months, and showed a reduction of about 36% at the end of 1 year. By the end of the one-year follow-up, IOP in all eyes was successfully controlled below 20 mm Hg.

In a recent review of interventions for angle-closure glaucoma, Saw et al [223] pointed out that latanoprost can be recommended for LPI patients who respond poorly to LPI although conclusive evidence is yet to be found.

2. Main Hypothesis and Aims of the PhD Project

The main purpose for this PhD project is to examine the immediate and longitudinal changes in the anatomical configuration of anterior chamber angle following laser peripheral iridotomy in treated and untreated eyes of primary angle-closure suspects. We therefore hypothesise that: in eyes treated by LPI, ACA is anatomically widened immediately after the laser treatment. The angle configuration will then remain stable during long-term follow-up after LPI.

The main research hypothesis will be tested through the following specific research objectives using data gathered during the Zhongshan Angle-closure Prevention Trial (the ZAP trial, which is described below):

1. To describe the baseline characteristics of the study population, including: (1) demographics; (2) IOP; (3) refraction and ocular biometric measures; (4) angle configurations assessed using gonioscopic findings and quantitative measurements of images acquired by anterior segment optical coherence tomography;

2. To investigate longitudinal changes in the angle configuration of PAC (assessed using gonioscopic findings and quantitative measures of AS-OCT images) by: (1) Measuring changes in angle configurations immediately following LPI; (2)

Assessing factors potentially associated with the magnitude of immediate change in angle configurations after LPI; (3) Examining the trend for longitudinal changes in angle configurations after LPI during the long-term follow-up; (4) Performing an association analysis of longitudinal changes in angle configurations of PACS (or, alternatively referred in this thesis as PAC suspect) following LPI.

3. To evaluate the association between dynamic anatomical features of the iris in eyes of PAC suspects by: (1) Describing baseline characteristics of iris dynamic behaviours in PAC suspects; (2) Investigating changes in iris dynamic behaviours after the elimination of pupillary block by LPI.

4. To investigate features of ACA-related anatomical structures in eyes of PAC suspects with persistent angle-closure following LPI, by qualitative assessment of anterior segment images acquired using ultrasound biomicroscopy.

5. This research will also describe the characteristics of baseline IOP distribution, and the association between IOP and angle configurations in eyes of PAC suspects.

3. Brief Introduction to the Zhongshan Angle-closure Prevention Trial

The Zhongshan Angle-closure Prevention Trial (the ZAP trial) is a collaborative research project between Moorfields Eye Hospital/University College London in the United Kingdom, Zhongshan Ophthalmic Center (ZOC)/Sun Yat-Sen University in China, and Wilmer Eye Institute/Johns Hopkins University in the United States of America. Both intervention and data collection were carried out in the Research Data Collection Centre at ZOC, which is a tertiary specialised hospital in Guangzhou, China. Guangzhou, the capital city of the Guangdong province located in the south pole of China, is one of the top three metropolitan cities in China. Guangzhou has a total population of approximately 32.3 million [224]. To ensure the safety and quality of the ZAP trial, a Data Monitoring and Safety Committee, a Trial Steering Committee and an Advisory Committee comprising of internationally renowned glaucoma specialists were established.

The ZAP trial was approved locally by the Ethics Committee of ZOC, and also received institutional review board approval from Moorfields Eye Hospital (via The London School of Hygiene and Tropical Medicine) and Johns Hopkins University. All study participants gave written informed consent both at the screening survey and before laser treatment. The study was conducted in accordance with the tenets of the World Medical Association's Declaration of Helsinki.

3.1. Main Research Question, Specific Aims and Study Design

The ZAP trial aims to assess whether laser peripheral iridotomy is safe and effective in preventing the development of precursors of PACG in a large cohort with high risk ocular biometric characteristics drawn from a representative population of urban Chinese people aged 50 to 70 years.

Specifically, this trial aims at:

(1) Determining if LPI prevents the development of peripheral anterior synechiae or elevated IOP in individuals with narrow angles.

(2) Identifying ocular parameters measured at baseline associated with developing acute or chronic angle-closure in untreated eyes.

(3) Comparing the rates of development of lens opacity and endothelial cell loss between treated and untreated eyes.

The ZAP trial was designed as a randomised controlled clinical trial. Participants identified as being PAC suspects and eligible for the study were treated by LPI in one randomly selected eye, with the fellow untreated eye observed in the trial as the control.

3.1.1. Sample Size and Power Considerations

Published data on the rate of progression of PACS eyes to PAC or AAC are limited. A population-based prevalence study in southern India reported a 2.2% prevalence of PACS [225] in people aged 40 years or older. In a follow up study [226] involving 50 of the 118 PACS cases (identified as eyes having 6 or more clock hours of angle circumference in which the pigmented or posterior trabecular meshwork was not visible under static gonioscopy, same as the definition used in the ZAP trial) identified at baseline, 11 (22%; 95% CI 9.8 to 34.2) were found to have developed PAC 5 years after the survey. Twenty eight of the 37 patients diagnosed as having PAC in the prevalence survey were also examined in the 5-year follow-up study. Eight (29%; 95% CI 12% to 45%) were identified to have progressed to PACG. All PAC patients identified in the prevalence survey were advised to undergo LPI when diagnosed. Only 1 of the 9 (11.1%) who underwent LPI developed progression to PACG compared to 7 of 19 (36.8%) who declined. In the current study, we plan to follow up the study participants for up to 60 months with an estimated 25% total incidence of progression to PAC in untreated eyes. Clinically we believe it is important to be able to detect a decrease in events as small as 30% from LPI prophylaxis. Assuming conservatively that the incidence of PAC or AAC in the untreated eyes is only 20%, we estimated the sample size needed was 614 individuals. Since the rate may be as low as 18% in the cases, the sample size was then inflated to 700 individuals, which represented 700 eyes per group (since one eye will be treated and the fellow eye will serve as the control). Estimating an attrition rate up to 20%, the target sample size was finally set

at 870 individuals.

3.1.2. Screening Survey and Recruitment

Recruitment into this trial commenced in September 2008. A total of 11,991 urban Guangzhou citizens aged 50 to 70 years were invited to participate in the screening survey. Individuals identified as PACS without any conditions meeting the trial exclusion criteria were regarded as being eligible for the trial.

3.1.2.1. Definition of Primary Angle-closure Suspect in the ZAP Trial

In the ZAP trial, PACS was defined as those who had 6 or more clock hours of angle circumference in which the posterior, usually pigmented, trabecular meshwork was not visible under static gonioscopy in both eyes, without IOP elevated to > 21 mmHg, no peripheral anterior synechiae (, no glaucomatous optic neuropathy and no evidence of anterior segment ischemia from a previous acute IOP increase.

3.1.2.2. Trial Exclusion Criteria

Potential participants were excluded if they have evidence of primary angle-closure (eyes with anterior chamber angle configuration meeting the definition of narrow angle in PACS, but also with PAS and/or IOP > 21 mmHg), glaucomatous optic neuropathy, or if they had any of the following characteristics:

(1) Aged less than 50 years or more than 70 years

(2) Plans to move from the area within the following 5 years.

(3) Severe health problems precluding follow-up such as end-stage heart disease, kidney disease, or lung disease, or terminal cancer.

(4) Prior intraocular surgery or penetrating eye injury as observed by the clinician examining the subject (i.e., not per patient report).

(5) Media opacity preventing laser iridotomy (e.g. corneal opacity).

(6) Evidence of a prior acute angle-closure attack (the presence of iris whorling, focal iris atrophy, or glaukomflecken with a history of an acute red eye and decreased vision).

(7) People who were unable to give their own informed consent.

(8) People with an excessively high risk of AAC. These would be subjects who had a rise in IOP of > 15 mmHg after a 15-minute dark room prone provocative test (DRPPT).

(9) Best corrected visual acuity worse than 20/40 presumed due to cataract.

Detailed methodology of the ZAP trial was published elsewhere. [74] As summarised in Figure 2, in the screening survey, all participants were examined in the anterior and posterior segments of their eyes using Slit-lamp microscopy and indirect funduscopy. The limbal ACD was assessed using the modified van Herick grading system [66], participants with the van Herick score of either eye being 25% or lower were sent for further anterior chamber angle assessment using gonioscopy. Only those who were

identified as PACS and gave written informed consent for the intervention were enrolled. All participants underwent a DRPPT as part of the enrolment tests. Those who had an IOP increase greater than 15 mmHg above baseline during DRPPT were excluded. All eligible participants received LPI in 1 randomly selected eye, with the fellow eye serving as a control. Randomisation was carried out using a pre-generated list of random numbers. Each eligible participant was assigned a number according to their sequence of entering the study. Randomisation numbers and their corresponding eye assignment were generated at the data-monitoring centre at Wilmer Eye Institute and sent in sealed envelopes to the clinical data-collection centre at Zhongshan Ophthalmic Center. [74] Following the intervention by LPI, study participants were followed up for a minimum period of 36 months and will be followed up for up to 60 months.

3.1.3. Examinations at Baseline and Follow-up Visits

3.1.3.1. Baseline Examinations

In the screening survey, participants were rapidly assessed for potential eligibility at the very initial stage of the survey. If the van Herick limbal ACD score was > 25% in both eyes or if the IOP > 21mmHg, the participant was identified as being ineligible and was referred for a limited eye assessment for service purposes. Procedures that the study participants went through in the rapid screening included:

1. **Registration and Consent** – The following personal information of each participant was recorded: name, contact phone number, home address, place of origin, and the last 4 digits of the National Registration Identity Card (NRIC) number.

2. **Eligibility Questions** – Three questions were asked for a rapid identification of ineligibility for the trial. Participants who answered “yes” to any of the following questions were immediately discounted from trial eligibility, and were arranged to undergo a simplified set of examinations for service purposes:

   (1) Have you had previous intraocular ophthalmic surgery?

   (2) Have you previously been treated for glaucoma?

   (3) Do you have a serious (i.e. life threatening) disease?

3. **Autorefraction** (Topcon KR8800, Tokyo, Japan): Three measures were obtained for each eye. The average spherical lens power, cylindrical lens power and the axis of cylindrical lens were recorded.

4. **Visual acuity:** Presenting visual acuity and best corrected visual acuity were measured using the ETDRS (Early Treatment Diabetic Retinopathy Study) LogMAR E chart (Precision Vision, Villa Park, Illinois, USA).

Participants with presenting visual acuity (i.e. habitual distance visual acuity) less than < 6/12 were referred to a research optometrist for a subjectively refined refraction.

5. **Non-contact tonometry** – three measurements were taken on each eye using a non-contact tonometer (CT-80A, Topcon, Tokyo, Japan). Participants with high measurements from non-contact tonometry (> 24 mmHg) underwent another confirmatory measurement using Goldmann applanation tonometry.

6. **Slit-lamp examination** (Haag-Streit BQ-900): The Slit-lamp examination in the ZAP trial incorporated a modified van Herick LACD grade, examination for signs of secondary glaucoma, previous surgery and ischemic sequelae of angle-closure. People with a van Herick score ≦ 25% in either eye underwent gonioscopy. An undilated examination of the optic disc was carried out to exclude manifest glaucomatous optic neuropathy. Diagnosis of other visually significant pathology was conducted.

7. **Gonioscopy:** Gonioscopic examination was carried out following topical anaesthesia of the cornea, using an Ocular Instruments Magnaview or similar one-mirror or two-mirror Goldmann-type gonioscopy lens. The examination took place in a standardised dark room with low ambient

illumination (<1 lux illumination by digital light meter (measured using the Easy View model EAQ30; Extech Instruments, Inc., Waltham, MA)). Care was taken to avoid the beam falling on the pupil, in order to prevent alteration of the angle configuration.

If irido-trabecular contact (ITC) was identified, or the trabecular meshwork was not visible under static gonioscopy despite of multiple attempts to achieve an “over the hill view” when there was significant iris curvature, a dynamic examination was carried out by increasing the width and height of the slit light beam, as well as increasing brightness. In dynamic gonioscopy, participants were asked to look directly towards the mirror of the gonioscopic lens, bringing the adjacent rim of the gonioscopic lens over the central cornea. Pressure was exerted on the rim of the gonioscopic lens in order to indent the central cornea. If ITC was satisfactorily reversed in all areas, the range of appositional ITC was recorded. If not, a dynamic examination with a 4-mirror gonioscopic lens was carried out, before synechial angle closure (i.e. peripheral anterior synechiae, PAS, see Figure 3) was recorded. The height and width of synechial closure was recorded. PAS was defined as acquired adhesions of the iris to the corneoscleral wall crossing the scleral spur for a width of 1 clock hour or more, causing tenting of the peripheral iris. Iris stromal pigment on the surface of the trabecular meshwork was graded according to standard photos. If trabecular meshwork could not be seen because of marked iris curvature, an attempt

would be made to achieve an “over the hill” view by tilting the lens towards the trabecular meshwork. Care was taken to avoid excessive tilting which may cause inadvertent corneal indentation.

8. **Anterior segment optical coherence tomography:** Horizontal and vertical scans of AS-OCT (Visante, Carl Zeiss Meditec, Dublin, CA) were performed to obtain images of the anterior chamber angle in 4 quadrants. The AS-OCT scans were carried out in the same standardised low ambient illumination at all study visits.

9. **Confirmatory examinations:** Participants identified as being potentially eligible by gonioscopy were then sent for a series of detailed examinations to confirm the eligibility for the ZAP trial. These examinations included:

(1) **Visual field testing**: Visual field testing was performed using the 24-2 SITA FAST program of a Humphrey Field Analyzer (Carl Zeiss Meditec, Oberkochen, Germany). Performance criteria required for an acceptable visual field test are: fixation losses – no specification; false negatives < 33%, false positives < 33%. For participants without glaucomatous optic disc appearance, a normal or borderline Glaucoma Hemifield Test (GHT) result was accepted. Otherwise a normal GHT result was required.

(2) **Specular Microscopy**: In order to determine if prophylactic laser iridotomy damages the corneal endothelium, a non-contact, semi-automated system (Topcon 2000P Specular Microscopy (Topcon, Tokyo, Japan)) that produces a digital image of the corneal endothelium was used to document the endothelial cell density, average cell size, hexagonality, and coefficient of variation.

(3) **Goldmann Applanation Tonometry**: IOP measurement by Goldmann applanation tonometry (attached to a Haag-Streit BQ 900 Slit-lamp (Haag-Streit AG, Koeniz, Switzerland)) was repeated to ensure that the subject does not have an IOP > 21 mmHg.

(4) **Dark Room Prone Provocative Testing (DRPPT):** The DRPPT was used to exclude the excessively high risk individuals from the study and to determine if response of the DRPPT was associated with outcomes. Following topical anaesthesia and a baseline IOP measurement using a Tonopen applanation tonometer (TONO-PEN XL, Medtronic, Florida, USA), the subject was placed face-down on a couch in a dark room for 15 minutes with the forehead resting on a soft pillow. The subject was accompanied by a research nurse and allowed to talk so as not to fall asleep. A second IOP measurement using the same method was performed after 15 minutes had elapsed. The measurement was made within 30 seconds of moving from

face-down position to upright in a lighted environment. Subjects who had an IOP rise above 15 mmHg from baseline were defined ineligible and offered laser treatment by LPI in both eyes.

3.1.3.2. Follow-up Examinations

After laser treatment, follow-up examinations were arranged for each participant at 2 weeks, 6 months, 18 months, 36 months and 54 months following LPI. The planned minimum period of follow-up was 36 months. Table 2 lists the scheduled visits and procedures of the examination during a follow-up period of 36 months in the ZAP trial. Apart from the above examinations for determination of eligibility or essential part of data collection across all visits, other examinations included:

1. **Ultrasound Biomicroscopy (UBM):** UBM examination was carried out in a dark room (illumination < 5 Lux) using an ultrasound biomicroscope (model UBM SW-3200, Suoer, Tianjin, China). One image of each quadrant and the central anterior chamber were acquired with the participant being in a supine position. The subjects were asked to fixate on a ceiling target using the contra-lateral eye. Five target markers (made from fluorescent paper, 5cm x 5cm in size) were set up on the ceiling to guide the patients' direction of gaze for scanning in the superior, inferior, nasal and temporal quadrants so that the angle between the gaze direction and the measurement axis was standardised to 20 degrees and

accommodation was controlled. Methylcellulose 2% and normal saline were used as coupling agents and topical anaesthesia was achieved before the scanning. The probe was always perpendicular to the ocular surface. To reveal the relationship between the iris and the ciliary body, care was taken to ensure the radial perpendicular UBM scans be obtained through a typical ciliary process. The gain was set to between 80 to 105 dB in order to have a clear display on the structure and minimise the ultrasound. The criteria for acceptable images were: clear visualisation of the scleral spur, angle, ciliary body and a half chord of the iris. An attempt was made to keep the tangent line of the anterior surface of the lens horizontal in order to ensure standardisation of the image appearance.

2. **Questionnaire**: A questionnaire interview was carried out acquiring information related to: demographics, education level, housing, income, occupation as well as questions designed to elicit a history of previous symptomatic angle closure. Family history of glaucoma was recorded. There were also questions covering past ophthalmic, medical, surgical and allergic history. Any medication currently being used was also noted.

3. **Anthropometry:** Height was measured with the subject standing up straight without shoes and recorded in meters. Weight was measured with the patient dressed but after removing coats and shoes and was recorded in kilogrammes. BMI was derived from the ratio of the subject's weight (in kilogrammes) divided by

the square of the subject's height (in metres) and recorded in kilogrammes per square meter. The scales (Height scale: SECA202, Saikang, Hangzhou, China; Weight scale: RGZ-120, Jiangsu, China) used for measuring anthropomorphic parameters were calibrated on a daily basis.

4. **Ocular Biometry:** ocular biometric measures including axial length, central anterior chamber length and lens thickness were measured using A-mode ultrasound (Echoscan US1800; Nidek Corp, Gamagori, Japan).

5. **Lens Opacity Classification System III (LOCS III) grading:** Pupils of both eyes were dilated with tropicamide 1% at two weeks after LPI in order to allow for slit-lamp lens grading. A modified version of the LOCS III grading system was used [21-23]. Briefly, the system grades nuclear colour (NC), nuclear opalescence (NO), cortical (C) and posterior sub-capsular (PSC) cataract according to various objective measures of colour, density and area. Standard photographs were used to objectively grade interval measures of colour, density and opacity area.

3.1.4. Laser Peripheral Iridotomy

LPI was performed using an Nd;YAG laser (Visulas YAG III, Carl Zeiss Meditec, Dublin, CA, USA). One drop of brimonidine 0.15% and pilocarpine 2% were instilled in the intervention eye 15 minutes prior to treatment in order to reduce IOP spikes and to thin

the iris, making the iridotomy procedure more straightforward. Patients were treated in the superior region (from 10 to 2 o'clock) in an area where the iris appeared thinnest (preferably in a crypt). Using the YAG laser, starting at an initial setting of 1.5 mJ, all iridotomies were performed using an Abraham lens (Ocular Instruments, Bellevue, WA, USA) to focus the laser beam and minimise possible adverse events. The minimum size of an iridotomy was 200 μm (0.2 mm) in diameter, judged using the 0.2 mm spot on a slit-lamp. The number of applications, the energy level and the total energy used were recorded. IOP was re-measured one hour after completion of the procedure. Individuals who had a post-LPI IOP of greater than 30 mmHg but less than 40 mmHg were given a second drop of brimonidine and 25mg methazolamide (if there was no contraindication), and were discharged with a prescription of methazolamide 25mg for oral administration three times a day for 2 days. IOP was re-evaluated after 2 days. If the post-LPI IOP was above 40 mm Hg, the participant was kept in the research clinic for an additional hour after receiving the additional medications to re-check the IOP. If the IOP began to fall, the participant would be discharged and examined the following morning. If the IOP rose further, referral to a glaucoma specialist was made for further management. All treated subjects were sent home on dexamethasone 0.1% eye drops hourly for 24 hours, and then four times a day for one week after the procedure.

3.1.5. Study Endpoints

In the minimum period of 36 months in the ZAP trial, study participants were followed

up to identify the following 3 specific endpoints

(1) Elevated intraocular pressure (IOP) > 24 mmHg on two consecutive measurements on separate days;

(2) Newly developed PAS for at least 1 clock hour range;

(3) An episode of symptomatic (“acute”) angle closure.

3.2. Assessment of Anterior Chamber Angle Configuration

The width of the anterior chamber angle was assessed using both evaluation under static gonioscopy and quantitative measurements from images acquired by AS-OCT (see **3.1.3** for details of the methods used for gonioscopy and AS-OCT imaging).

The width of anterior chamber angle was assessed under static gonioscopy using the Shaffer grading system: angle width in each quadrant was estimated as the angle in degrees between a tangent line to the surface of the trabecular meshwork and another tangent line to the peripheral third of the iris, and then was recorded in 5-point categories (Shaffer grades 0 to 4 correspond to 0°, 10°, 20°, 30°, and ≧40°, respectively). The range of iridotrabecular appositional contact as well as the number of quadrants in which the posterior/pigmented trabecular meshwork was not visible under static gonioscopy was also recorded. Peripheral iris profile was evaluated under gonioscopy and classified as being regular, steep, plateau or queer.[227]

Spaeth grades, assessed based on the point where iris inserts onto the ciliary body or the internal lining of the eyeball, was also recorded. When the iris touches the corneal endothelium anterior to the trabecular meshwork around the Schwalbe's line, the Spaeth grade was designated as 'A' (indicating 'anterior'). When the point of contact is behind the Schwalbe's line in the area of the trabecular meshwork, the symbol is 'B' (indicating 'behind' the Schwalbe's line). When the iris root is at the level of the scleral spur, the designation is 'C' (standing for the letter 'c' in 'sclera'). The symbol 'D' (standing for 'deep') means a deep angle recess in which the anterior ciliary body is visible. The final category is designated as 'E' (standing for 'extremely deep'), which indicates that the iris joins the ciliary body in an extremely posterior position, allowing an unusually wide range of ciliary body to be seen.

The AS-OCT images were quantitatively assessed using custom software (the Zhongshan Angle Assessment Program[90]) to measure angle opening distance (AOD), trabecular-iris space area (TISA) and angle recess area (ARA). Image analysis was performed by 3 certified graders who were masked to the intervention assignment and study visit. A set of 200 images from 200 eyes (of 200 individuals) were randomly selected and graded by all 3 graders independently. Good inter-grader agreement was shown by high intra-class correlation coefficient (ICC). The AOD was defined as the length of a line drawn from the anterior surface of the iris to the corneal endothelium perpendicular to the plane of the surface of the trabecular meshwork at 250 μm, 500

μm and 750 μm from the scleral spur (AOD250, AOD500 and AOD750, respectively).[82] The TISA was defined as the trapezoidal area between: anteriorly, AOD500 or AOD750 (TISA500 and TISA750, respectively); posteriorly, a line drawn from the scleral spur perpendicular to the plane of the inner scleral wall to the anterior surface of the iris; superiorly, the inner corneoscleral wall; and inferiorly, the anterior surface of the iris.[85,91] The ARA was defined as the triangular area between the anterior iris surface, the inner corneoscleral wall and a line perpendicular to the AOD750.[18] Iris curvature (alternatively named “iris convexity”) was defined as the maximum perpendicular distance between the posterior iris surface and the line connecting the most peripheral and the most central points of iris pigment epithelium relative to the pupillary centre. The IT750 was defined as perpendicular iris thickness measured at 750 μm from the scleral spur. Mean pupil diameter of the horizontal and vertical scans acquired in the dark was also recorded for each eye. Lens vault, defined as the perpendicular distance between the anterior pole of the crystalline lens and the horizontal line joining the two scleral spurs,[228] was also measured using AS-OCT images.

Table 1 Inter-grader Agreement for Quantitative Grading of AS-OCT Scans

AS-OCT§ Measures	Intraclass Correlation Coefficients		
	Grader 1 vs 2	Grader 2 vs 3	Grader 1 vs 3
lAOD500§	0.77	0.79	0.80
lTISA750§	0.80	0.85	0.86
lARA§	0.89	0.91	0.91
lIT750§	0.85	0.85	0.79
lIT2000§	0.83	0.90	0.86
lIAREA§	0.93	0.93	0.93
lICURV§	0.89	0.86	0.85
rAOD500§	0.85	0.85	0.83
rTISA750§	0.92	0.90	0.89
rARA§	0.90	0.91	0.89
rIT750§	0.79	0.76	0.83
rIT2000§	0.86	0.86	0.90
rIAREA§	0.93	0.92	0.94
rICURV§	0.88	0.87	0.88
ACD§	1.00	1.00	1.00
LENSVAULT§	0.86	0.91	0.88

§ AS-OCT: anterior segment optical coherence tomography; lAOD/rAOD: angle opening distance on the left or right side of the scan; lTISA/rTISA: trabecular-iris space area on the left or right side of the scan; lARA/rARA: angle recess area on the left or right side of the scan; lIT/rIT: iris thickness on the left or right side of the scan; lIAREA/rIAREA: iris cross-sectional area on the left or right side of the scan; lICURV/rICURV: iris curvature on the left or right side of the scan; ACD: anterior chamber depth; LENSVAULT: lens vault

Table 2 Examinations at Baseline and Follow-up Visits in the ZAP Trial

Time of Follow-up	Visual Acuity	Auto-refraction	NCT†	van Herick Scoring	Slit-lamp& Fuduscopy	Gonioscopy	AS-OCT†	Fundus Photography	Specular Microscopy	GAT†	LOCSIII	Visual Field Test	UBM†
Baseline	√	√	√	√	√	√	√	√	√	√	√	√	√
Post-LPI† 2 Weeks					√	√	√	√		√	√		√
Post-LPI† 6 Months	√	√	√	√	√	√	√	√	√	√			
Post-LPI† 18 Months	√	√	√	√	√	√	√	√	√	√	√	√	√
Post-LPI† 36 Months	√	√	√	√	√	√	√	√	√	√	√	√	√

† NCT: non-contact tonometry; AS-OCT: anterior segment optical coherence tomography; GAT: Goldmann Applanation Tonometry; UBM: ultrasound biomicroscopy; LPI: laser peripheral iridotomy

Figure 1 An overview of the Administration, Monitoring and Coordination Infrastructures in the ZAP Trial

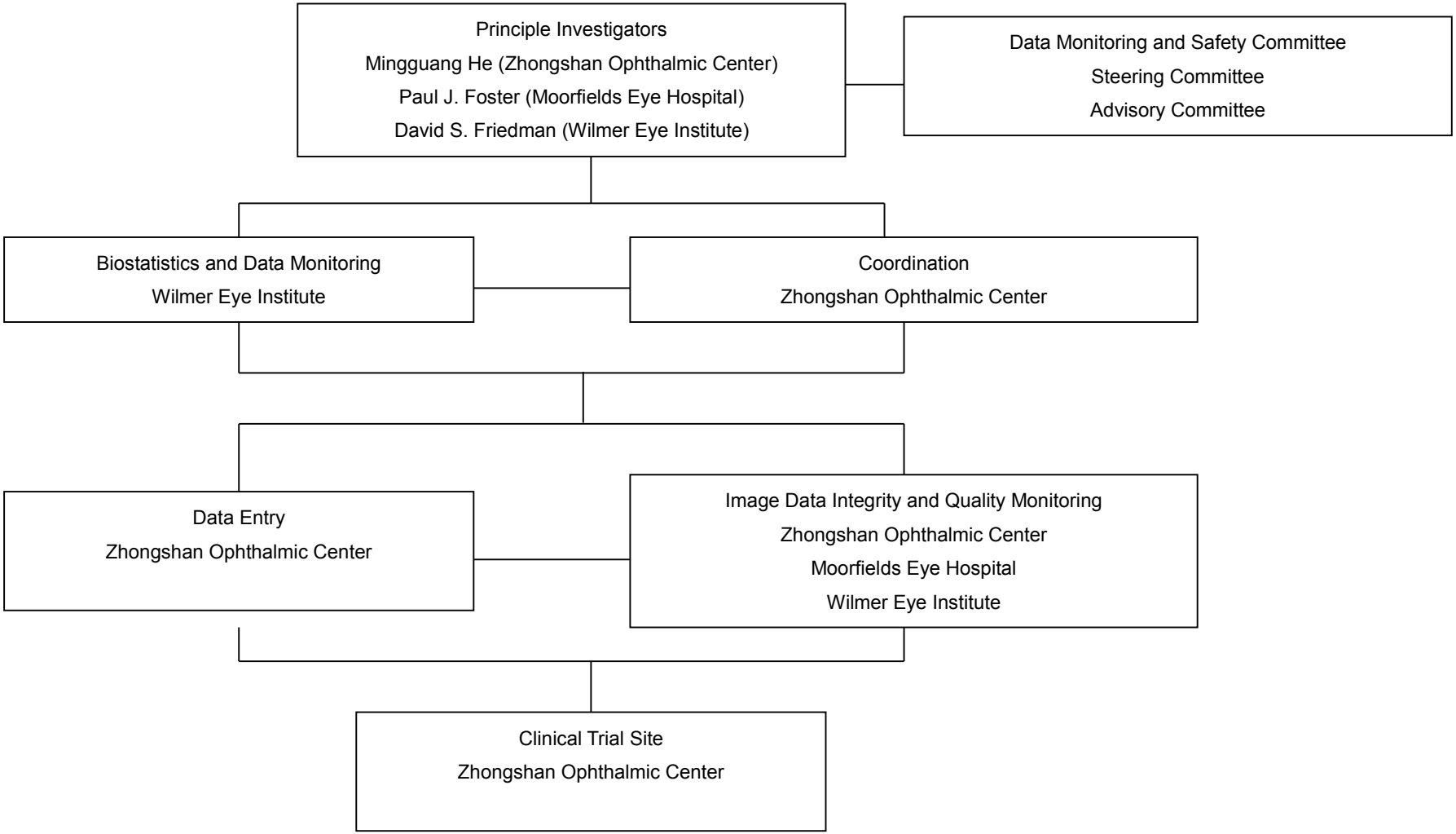
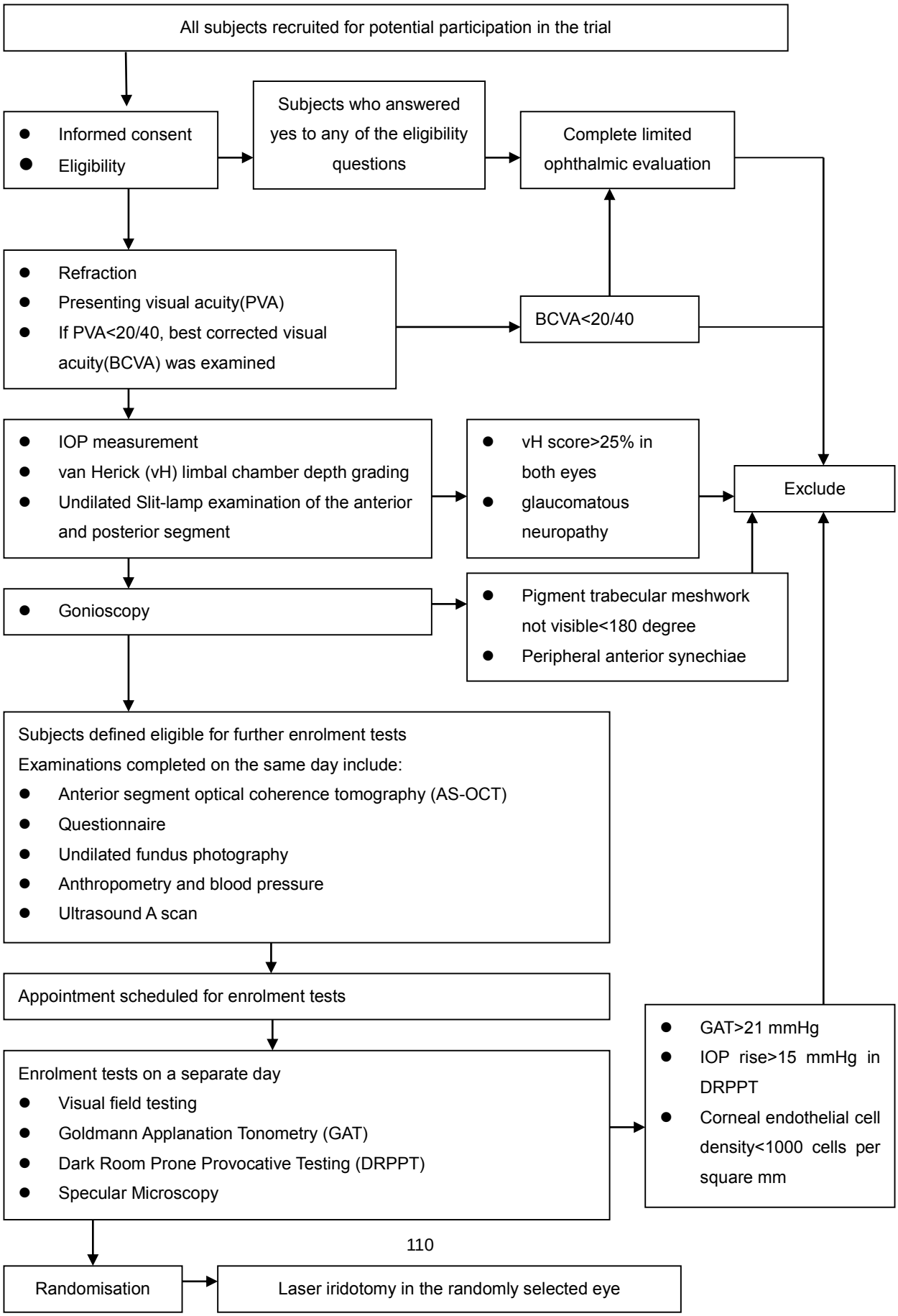


Figure 2 Screening, Enrolment, and Intervention in the ZAP Trial



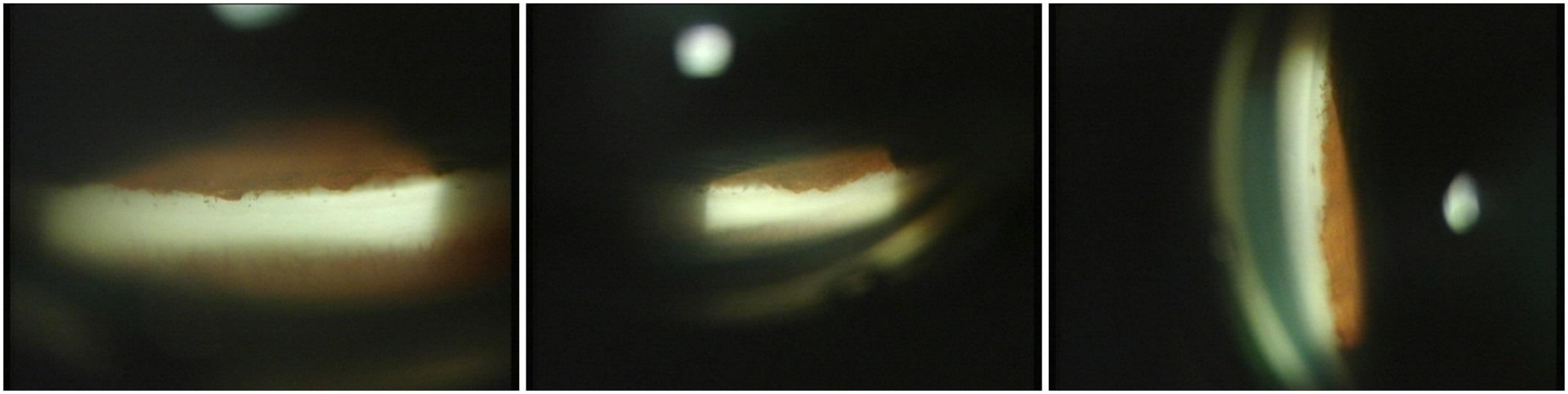


Figure 3 Standard Photos Used in the ZAP Trials for Identifying Peripheral Anterior Synechiae

4. A Summary of the Candidate's Research Activities related to this PhD Program

4.1 I, as the PhD candidate, started working as the trial manager and one of the co-investigators in the ZAP trial since September 2008. My responsibilities during the field work from September 2008 to April 2011 included: day-to-day data collection, making recruitment strategies, making follow-up rate maintenance strategies, patient flow management, and database management.

4.2 Research activities during the PhD program included:

(1) Designing of the PhD research project;

(2) Training image graders and organising inter-grader agreement tests;

(3) Performing data cleaning and statistical analysis of quantitative image grading results in the ZAP trial;

(4) Qualitative grading of the UBM images included in the PhD research;

(5) Statistical analysis and publication of secondary outcomes of the ZAP trial (refer to "Personally Published Paper Pertinent to this Thesis")

5. Anatomical Features of the Anterior Chamber Angles in Primary Angle-closure Suspects

5.1. Introduction

Glaucoma is one of the leading causes of blindness in the world. It has been predicted that by the year 2020, 80 million people will have glaucoma, among which around 11 million will be blind from glaucoma in both eyes. Half of these binocularly blind people will be blinded by PACG.[1] Even though PACG is much less common than POAG among whites, blacks, and Hispanic people, it is likely that PACG accounts for a significant proportion of glaucomatous loss of visual function given the potentially greater morbidity of this disease. Not only may acute attacks of primary angle-closure cause severe loss of vision, more chronic (and usually asymptomatic) forms of this condition can also result in severe glaucomatous optic nerve damage and consequent irreversible damage to visual function. While only about 26% of those with primary glaucoma will have PACG by 2020, the number of blind patients caused by PACG is estimated to be almost equal to that by POAG.[1]

PACG is a potentially detectable and preventable disease. There is broad-based consensus that PACG is one of the leading global priorities for the prevention of blindness. While PACG clearly is an important disease among all racial groups living

in the UK, the prevalence is greatest among East Asians. It has been projected that by the year 2020, the proportion of all those with PACG who live in Asian regions will increase to 87.6%.[1] China is home to the majority of people with PACG worldwide, and apparently is the ideal location for carrying out research programs on the prevention, screening and treatment of PACG.

Previous prevalence study has suggested that a predominant part of primary angle-closure cases in China present as chronic asymptomatic conditions. Up to 10% of elderly Chinese have anatomical risks for developing angle-closure.[23] A good understanding of the anatomical features and risk factors for PACG is of potential importance for early recognition and effective prophylaxis of this potentially preventable disease. Certain anatomical features of ocular structures may contribute to the predispositions for primary angle-closure. Shallower central anterior chamber depth (ACD), shorter axial length, greater lens thickness and smaller radius of corneal curvature have previously been associated with narrow angle configuration and higher risk for developing primary angle-closure. [139-143] Several studies recently revealed a possible association between central anterior chamber depth and adult anthropometry. In a population-based cross-sectional survey, Wong et al[136] found a tendency for taller persons to have longer AL, deeper ACD, longer vitreous cavity distance, flatter corneas and thinner lenses, as compared to shorter persons of similar weight, age, sex and socioeconomic status. Weight, however, was found to have no associations with biometric measurements after controlling for age, sex, height and socioeconomic

factors. In another population-based study involving 3,191 subjects, a significant association was found between limbal ACD and shorter body stature [144]. Although shallow ACD has been widely recognised as the leading anatomical risk factor for primary angle-closure and a potential surrogate indicator that is closely related to narrower angle width [5,36,131,132], observation under gonioscopy still remains the gold standard for the diagnosis of occludable angle status (which, disputably, is regarded to be more suitably named as “narrow angle” status, i.e. PACS) or primary angle-closure.

This section gives a description of some basic anatomical features of the anterior chamber angles in asymptomatic PAC suspects of Chinese ethnicity. Results of investigations on several possible associations of narrow angle configurations are also discussed.

5.2. Methods

5.2.1. Study Subjects

5.2.1.1. Analysis of Anatomical Features of Anterior Chamber Angle and Associations of Angle Configurations of PACS Eyes in the ZAP Trial

Study subjects in the analysis of anatomical features of anterior chamber angles in

PACS in the ZAP trial are urban residents in the Guangzhou city aged between 50 and 70 years. They were recruited from a screening survey that involved 11,991 participants from September 2008 to August 2010. PACS eligibility for this study was defined as those who had 6 or more clock hours of angle circumference in which the PTM was not visible under static gonioscopy in both eyes, without IOP elevated to above 21 mmHg, no PAS, no GON and no evidence of anterior segment ischemia from a previous acute IOP increase. See 3.1.2 for detailed inclusion and exclusion criteria employed in the ZAP trial.

5.2.1.2. Analysis of Associations between Narrow Angle and Adult Anthropometry

Study subjects in the analysis on associations of the existence of narrow angle status were recruited from a population-based cross-sectional survey (the Liwan Eye Study) in southern China. Linear regression analysis on associations of the quantitative angle measurements in PACS eyes were performed based on data from the ZAP trial. Detailed methodology of the Liwan Eye Study has been reported elsewhere.[8, 9] In brief, subjects aged 50 years and above were enrolled from the Liwan District of Guangzhou using cluster random sampling. In total, of the 1,864 residents identified eligible in the clustered sampling, 1,405 individuals who participated in the cross-sectional survey were examined. Among these 1,405 participants, only phakic subjects with anthropomorphic measurement data available were included in the current analysis.

Socioeconomic information was collected by a trained interviewer using a standard questionnaire. A handheld autorefractor (ARK-30; Nidek Corp, Gamagori, Japan) was used to measure noncycloplegic refraction. Axial ocular biometric parameters including central ACD, lens thickness and axial length were measured using A-mode ultrasound (Echoscan US1800; Nidek Corp, Gamagori, Japan).

5.2.2. Measurement of Anthropometric Parameters

Detailed methodology for measuring adult anthropometry was described in 3.1.3.2. BMI was derived from the ratio of the subject's weight divided by the square of the subject's height and recorded in kilogrammes per square meter. The scales (Height scale: SECA202, Saikang, Hangzhou, China; Weight scale: RGZ-120, Jiangsu, China) used for measuring anthropomorphic parameters were calibrated on a daily basis.

5.2.3. Gonioscopy

Detailed methods regarding gonioscopy in the Liwan Eye Study have been reported elsewhere previously [9], which is similar to the methods described in 3.1.3.1. Angle width was estimated in the superior and inferior quadrants as the angle in degrees between a tangent line to the surface of the trabecular meshwork and another tangent line to the peripheral third of the iris, and then recorded in five-point categories (0°,10°,20°,30°, and ≥40°). Mean angle width of each eye was calculated from the

angle width of the superior and inferior quadrants. All gonioscopic examinations in this study were carried out by an experienced specialist-trained ophthalmologist.

5.2.4. Definitions of Narrow Angle

The status of narrow anterior chamber angle in this study referred to eyes in which the PTM was not visible in at least 3 quadrants (i.e. 270° circumference) under static gonioscopy.

5.2.5. Statistical Analysis

5.2.5.1. Analysis of Anatomical Features of Anterior Chamber Angle and Associations of Angle Configurations of PACS Eyes in the ZAP Trial

Baseline measures of angle configuration (including measurements from gonioscopic findings and quantitative analysis of AS-OCT images) were compared between men and women in eyes treated and untreated by LPI using Mann-Whitney tests (also named Wilcoxon rank-sum tests). Inter-quadrant comparisons of angle configuration measurements were performed using the Kruskal-Wallis tests.

5.2.5.2. Analysis of Associations between Narrow Angle and Adult Anthropometry

Only right eye data were included in the current analysis. Mann Whitney U tests and Chi-square tests were used for comparison of demographic, refractive, axial ocular biometric and socioeconomic parameters between included and excluded phakic subjects. The tests for trend across ordered groups were used to examine the correlation between angle width and different quartile levels of anthropomorphic measures. Univariable and multivariable logistic regression models were used to assess the association between occludable angle and anthropomorphic measures.

All statistical analysis was performed using Stata/SE 13.1 (StataCorp, College Station, TX, USA).

5.3. Results

5.3.1. Demographics, Ocular Biometry and Anthropometry of Primary Angle-closure Suspects in the ZAP Trial

In the screening survey of the ZAP trial, 11,991 urban Guangzhou citizens aged 50 to 70 were examined, among which 1,113 were identified as potentially eligible and 889 were successfully enrolled into the trial. So far (up to May 2015), in the 889 participants who have been treated with LPI in one randomly selected eye, 885 completed follow-up visits at 2 weeks after LPI (attrition rate: 0.45%), 863 completed follow-up visits at

6 months after LPI (attrition rate: 2.92%), 838 completed follow-up visits at 18 months after LPI (attrition rate: 5.74%), 778 received follow-up examinations at 36 months after LPI (attrition rate: 12.49%), and 557 have returned for follow up at 54 months following LPI (other participants still have not reached the time window for the post-LPI 54-month follow up visit).

Of the 889 primary angle-closure suspects who gave consent and received laser treatment, 152 were men and 737 were women. Men were generally older than women (men vs women, 61.40±5.09 years vs 58.87±4.88 years, *P*<0.001).

As shown in Figure 4, the most densely distributed age group of female participants in the ZAP trial is the 55-to-59-year age group. Out of 737 female participants at baseline, 251 (34.1%) were aged between 55 to 59 years, whereas only 25.7% of male participants (39 out of 152) belonged to this age group. In men, the proportion of individuals aged between 60 to 64 years (52 out of 152, 34.2%) is comparatively larger than those of other age groups.

Table 3 summarises the refractive status, ocular biometrics and anthropometry of the treated and untreated control eyes of male and female participants. Apart from the inter-gender difference in axial length (*P*<0.001 in both treated and untreated eyes), central anterior chamber depth of untreated eyes (*P*=0.005, only in untreated eyes), lens thickness (*P*=0.001 and 0.037 in treated and untreated eyes respectively), height

(*P*<0.001), weight (*P*<0.001) and BMI (*P*=0.022), no statistically significant inter-gender differences were found in other refractive and ocular biometric measures. In a general comparison without stratification by sex, no statistically significant differences in spherical equivalence, central ACD, axial length or lens thickness were found between treated and untreated eyes.

5.3.2. Baseline Characteristics of the Anterior Chamber Angle in Primary Angle-closure Suspects

Table 4 summarises anatomical features of anterior chamber angle of PACS eyes at baseline in eyes treated and untreated by LPI. Comparing gonioscopic findings between men and women, ACA of women appeared to have relatively narrower configuration, which was reflected by significantly smaller mean angle width calculated from Shaffer grades and greater total number of quadrants in which PTM was not visible. Similarly the baseline range of appositional iridotrabecular contact was also found to be significantly wider in untreated eyes of female participants compared to males. These gonioscopic findings were in accordance with limbal ACD assessed using modified van Herick scores. In both treated and untreated eyes of women, the proportions of eyes with a van Herick score of 5% and 15% are higher compared to men. The inter-gender difference in the distribution of limbal ACD between men and women was statistically significant in both treated and untreated eyes. However, the statistically significant inter-gender difference in gonioscopic angle configuration was

not reflected in measurements from AS-OCT images. As shown in **Table 4**, although the values for linear AS-OCT measurements of angle width and TISA500 were smaller in both treated and untreated eyes of women compared to those of men, most of the inter-gender differences were not statistically significant.

Table 5 to Table 7 show comparison of baseline angle configurations in different quadrants of both treated and untreated eyes in men and women. Apart from untreated eyes in men (in which no significant difference in angle width was detected between the nasal and inferior quadrants), gonioscopic angle width measured in four quadrants followed the same sequence, namely: inferior > nasal > temporal > superior. The inter-quadrant differences in baseline gonioscopic angle width of both treated and untreated eyes of men and women were statistically significant. This is also in accordance with other gonioscopic findings including Spaeth Grades (with “A” and “B” representing PTM not visible under static gonioscopy) and the range of appositional iridotrabecular contact. In AS-OCT images, however, the above rule/sequence did not apply to quantitative measurements including AOD250, AOD500, AOD750, TISA500, TISA750 and ARA. In the same cohort of participants, when assessed using quantitative measurements in AS-OCT images, angle width of different quadrants did not seem to follow a trend as consistent as with gonioscopic findings, although the superior remained to be the relatively narrowest quadrants for all quantitative AS-OCT measures. And the temporal quadrant in AS-OCT images was comparatively widest for most AS-OCT measurements.

5.3.3. Association between Angle-closure Narrow Angle and Adult Anthropometry

Data for this part of research were collected from a previous epidemiological study on glaucoma among urban elderly Chinese in the same geographic area of China (the Liwan Eye Study [23,229], Guangzhou, China).

Of the 1,358 phakic subjects examined, 912 (67.2%) had anthropometry data available and were included in the current analysis. Included and excluded subjects were similar in terms of sex, education level and refractive status. Compared to those excluded, the included subjects were younger (median age 65 years vs. 68 years, $P<0.05$) and had slightly shallower anterior chamber depth (2.66±0.33 mm vs. 2.80±0.31 mm, $P<0.05$).

A higher proportion of individuals with lower body weight and lower body height had narrow angles (**Table 8**). The lowest quartiles of weight, height, and BMI were significantly associated with narrower angle width. In univariate logistic regression analysis, older age, female gender, shorter body height, lower body weight, lower BMI, smaller axial length, shallower ACD, more hyperopic refractive error were all significantly associated with higher risk for having narrow angle (See 5.2.4 for definition). Higher education level (i.e. middle school or college education, as compared to no formal education or primary school education), however, was

significantly associated with lower risk for having narrow angle (**Table 9**).

In multiple logistic regression analyses, to avoid collinearity, BMI and weight were not included in the same regression model. As shown in **Table 10**, the association between lower BMI and narrow angle status remained statistically significant, after adjusting for height, age, sex, education level, axial length and ACD. Similar results were seen in the multivariable regression model assessing the association between weight and narrow angle. Apart from anthropometric measures, shorter axial length and shallower central ACD remained to be significantly associated with narrow angle status in multiple logistic regression models.

As shown in **Table 11**, interestingly, the association between lower body height and higher risk for having narrow angle remained statistically significant following adjustment of sex and age in the logistic regression models separately. The association also remained significant when only ocular biometric measures were included in the regression models. When both age and sex were adjusted, however, significance of the association disappeared (**Table 11**). Likelihood ratio test showed significant interaction between sex and age in multiple logistic regression models examining the association between narrow angle status and height with sex and age included as independent variables (P<0.001).

In a sex-stratified multiple logistic regression models examining the association

between BMI and narrow angle, statistical significance of this association was only present in women (**Table 12**). However, the interaction between BMI and sex in multivariable models was not statistically significant (Tests for interaction: *P*=0.33).

5.3.4. Associations of Angle Width in Primary Angle-closure Suspects

Table 13 and **Table 15** give results of univariate analyses on the associations of baseline angle configurations in untreated PACS eyes of both men and women. Similar results were shown in analyses on treated eyes. In univariate analysis, narrower angle width measured under static gonioscopy was shown to be significantly associated with shallower central ACD and greater lens thickness in PACS eyes of both men and women, whereas shorter axial length was significantly associated with narrower angle observed under static gonioscopy only in women. In univariate analysis, as shown in **Table 15**, smaller AOD500 and AOD750 were similarly associated with shallower ACD, shorter axial length and greater lens thickness. In multivariate analysis adjusting for demographic, anthropometric and socioeconomic factors, axial length and lens thickness were no longer significantly associated with angle width.

5.4. Discussion

Essential parts of statistical analysis in this thesis were stratified by gender, for the purposes of minimising the bias from the relatively large proportion of women in study

participants of the ZAP trial. The female-to-male ratio in the ZAP trial (Figure 4) was comparatively higher than that of previously reported PACS prevalence study in the same geographical area (5.0:1.9 in the 50-to-59 age group, and 13.7:8.7 in the 60-to-69 age group)[23], especially in the relatively younger age group. This might be partly explained by the different retirement age of men (60 years old) and women (50 to 55 years old) in China.

Results of quadrantal analysis of angle width in the current study are in good accordance with findings of previous prevalence study [230] which showed similar sequence in the dimension of drainage angle configuration among four quadrants of PACS eyes. In the 72 PACS eyes treated in the Liwan Eye Study [230], baseline gonioscopic assessment before LPI showed the proportions of eyes graded A or B in Spaeth grading system (representing PTM not visible under static gonioscopy) to be: 98.5% superiorly, 85.7% temporally, 75.7% nasally, and 57.1% inferiorly. This is in accordance with findings in the current research on quadrantal relationship of angle width assessed using gonioscopy, i.e. inferior > nasal > temporal > superior. Compared to gonioscopic findings, in AS-OCT scans, the configuration of temporal and nasal drainage angle in PACS eyes were relatively wider than the other two quadrants. This may offer a possible explanation of previously reported good diagnostic performance of quantitative measurements of temporal and nasal (especially temporal) angles in AS-OCT images [231].

Findings of the current study provide further supporting evidence to the previously reported close association between ACD and primary angle-closure (as summarised in 1.4.5). Central ACD was significantly associated with the existence of narrow angle status (in other words, the incidence of PACS). The relationship was also revealed by linear regression analysis as significant quantitative associations. Anthropometric measures, however, were only found to be associated with the risk for having narrow angle status without significant linear associations with quantitative measures of the angle width.

To briefly summarise findings described in 5.3.3, individuals with lower body weight and lower body height had a higher likelihood of having narrow anterior chamber angles. In multiple logistic regression models adjusting for height, age, sex, central anterior chamber depth and axial length, lower BMI and weight were significantly associated with greater risk for narrow angle. When stratifying the multivariate analysis by sex, the association between lower BMI and narrow angle was statistically significant only in female subjects.

Our findings are in agreement with those of a previous study in Singapore [10] which assessed the value of height for rapid assessment of risk for narrow angle. This study confirmed the findings by Wong et al [6] based on data from the same cross-sectional survey that decreased adult body height was significantly associated with a shallower ACD. However, after adjusting for age and sex, adult height was not significantly

associated with narrower angles. [10] Another community-based cross-sectional study of predominantly Chinese subjects reported no significant association between height and narrow angle. [11] In the current analysis, when only adjusting for sex, height remained significantly associated with narrow angle. The association between height and narrow angle disappeared when both age and sex were included in the regression model. This suggests that the association between height and narrow angle might largely result from the confounding effects from age. Significant interaction was also found between sex and age in the multiple logistic regression model containing height, sex and age as independent variables. It has been suggested that shorter body stature is associated with smaller ocular dimensions (mainly represented by shorter axial length) but not necessarily with narrow angle configuration.[10] Although shorter individuals may have relatively shallower anterior chamber and lens of greater central thickness, they may also have a steeper cornea and more convex anterior lens surface, both of which may contribute to widening the drainage angle in the peripheral anterior chamber.

The association between BMI and ocular traits has been studied in other population-based cohorts. Lower BMI was associated with smaller neuro-retinal rim area and larger cup-to-disc ratio [12] as well as thinner central retina and fovea. [13] In the current study, lower BMI was significantly associated with higher risk for having narrow angle after adjusting for age, sex, ACD, axial length and education level. One explanation for findings in this study might be the possible relationship between low BMI, especially at

earlier stages of life, and compromised development of the ocular structures. For example, children with lower BMI have been shown to have narrower retinal blood vessels. [14] There has been consistent evidence from previous studies showing that genetic factors are very important contributors to the variation of BMI.[15-17] Thus the possibility of compromised development in ocular anterior segment cannot be ruled out in individuals with lower BMI. It is also likely that BMI affects drainage angle configurations through the dynamic behaviours (e.g. changes of iris thickness and volume under different illumination) of the iris, since variations in BMI have recently been associated with different dynamic changes of the pupil.[18] Among individuals with lower BMI, certain changes in the thickness or volume of peripheral iris under different illumination could possibly make the anterior chamber angle appear to be comparatively narrower in dark illumination environment where gonioscopy is usually carried out. Further investigation is needed to unveil the characteristics of iris tissue and dynamic iris behaviours in individuals of different BMI.

In the current study, stratified analysis detected an association between BMI and narrow angle only in females. Female gender is associated with narrower drainage angle and higher incidence of angle-closure, especially among East Asians.[19, 20] Some believe that the relatively narrower angle configuration in women might result from a smaller overall ocular dimension and general body size. [21] Considering the age and ethnic background of female subjects in this study, lower BMI seemed to serve as another risk factor in this high-risk population for primary angle-closure.

Limbal ACD measured by the van Herick grading system [22] has been recognised as a useful tool for identifying individuals with narrow angles [23] and has also been shown to have good agreement with gonioscopy in assessing angle configuration.[24] However, in contrast to our findings, Xu and colleagues [7] found no significant association between limbal ACD and BMI in univariable analysis. In multivariable models with age, sex, height and weight included as independent variables, they found that limbal ACD remained significantly associated with body height but not with body weight. The differences between these findings and results of our study suggest that the association between adult anthropometry and limbal ACD may not be representative of the association between anthropomorphic measures and actual angle configuration directly observed under gonioscopy. Alternatively, given the limited data to support both findings, it is also possible that no real association exists.

Several limitations should be considered when interpreting findings of this analysis on associations of narrow angle status. In the Liwan Eye Study, anthropometry data were only available in 912 of the 1,358 phakic subjects examined in the population-based prevalence survey. Whilst excluded participants were relatively older and with deeper ACD, it is not likely that the associations we described would be systematically different in these people. Another limitation is that gonioscopy is dependent on the examiner's skills, experience and subjective judgements. Nevertheless, all gonioscopic examinations were carried out by the same experienced examiner in the Liwan Eye

Study, and by two fellowship-trained glaucoma specialists with high inter-examiner agreement (Kappa > 0.7 for all measures) in the ZAP trial. This would help minimise potential bias.

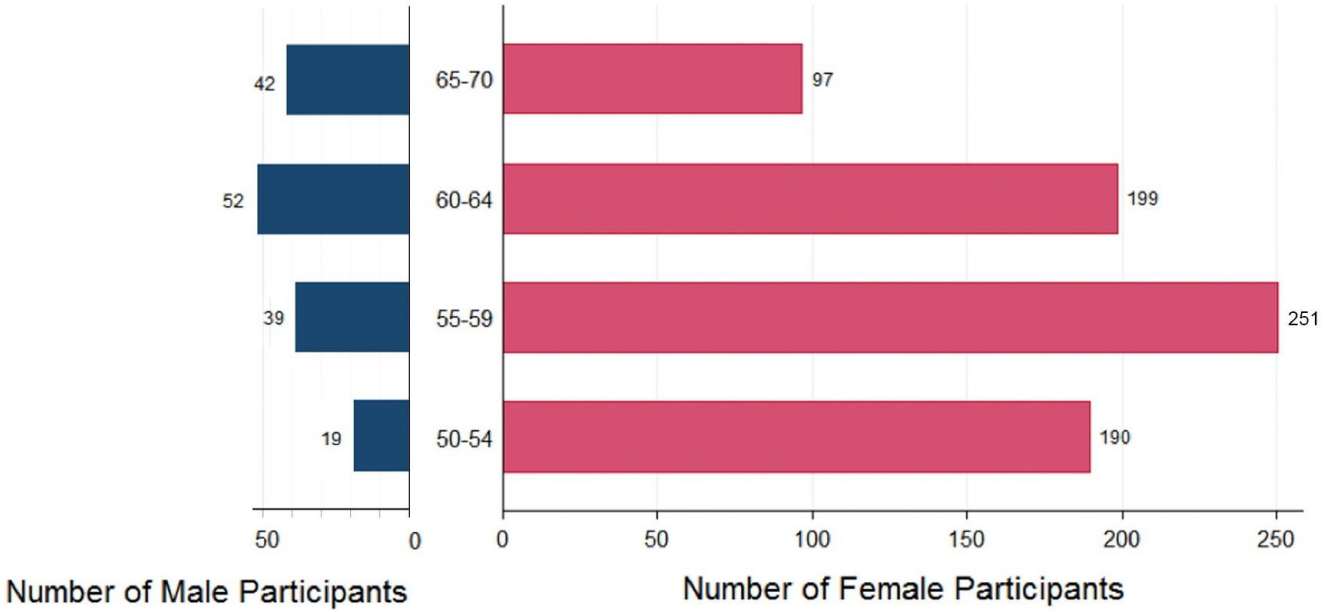


Figure 4 Age Distribution of Female Participants in the ZAP trial

Table 3 Refractive, Ocular Biometric and Anthropometric Measures of Treated and Untreated eyes in men and women

	Treated Eyes [Median (Interquartile range)]			**Untreated Eyes** [Median (Interquartile range)]		
	Men	**Women**	***P* value§**	**Men**	**Women**	***P* value§**
Spherical Equivalence (D)	1.75 (1.63)	2.00 (1.63)	0.12	2.13 (1.50)	2.00 (1.63)	0.07
Ocular Biometric Measures						
Central ACD† (mm)	2.54 (0.34)	2.56 (0.30)	0.97	2.63 (0.31)	2.54 (0.31)	0.005
Axial Length (mm)	22.75 (0.97)	22.46 (0.89)	<0.001	22.80 (0.88)	22.44 (0.90)	<0.001
Lens Thickness (mm)	4.96 (0.39)	4.86 (0.38)	0.001	4.91 (0.41)	4.88 (0.40)	0.037

Anthropometric Measures	**Men** [Median (Interquartile range)]	**Women** [Median (Interquartile range)]	***P* value§**
Height (m)	1.64 (0.07)	1.54 (0.07)	<0.001
Weight (kg)	64 (14)	55 (11)	<0.001
Body Mass Index (kg/m^2)	23.81 (3.77)	23.34 (4.26)	0.022

† ACD: anterior chamber depth; § Mann-Whitney tests

Table 4 Baseline Anatomical Features of Anterior Chamber Angle of PACS Eyes in Men and Women

	Treated Eyes [Median (Interquartile range)]			**Untreated Eyes** [Median (Interquartile range)]		
	Men	**Women**	***P* value§**	**Men**	**Women**	***P* value§**
Mean Angle Width (°)	15.0 (10.0)	12.5 (7.5)	0.002	15.0 (10.0)	12.5 (7.5)	<0.001
Appositional Iridotrabecular Contact (clock hour)	2.5 (4.0)	3.0 (5.0)	0.09	1.0 (3.0)	3.0 (5.0)	0.006
Number of Quadrants with PTM† not Visible under Gonioscopy [N(%)]						
2	23 (15.1)	52 (7.1)		28 (18.4)	59 (8.0)	
3	43 (28.3)	201 (27.3)	0.003	41 (27.0)	196 (26.6)	<0.001
4	86 (56.6)	484 (65.7)		83 (54.6)	482 (65.4)	
van Herick Score [N(%)]						
5%	4 (2.6)	27 (3.7)		3 (2.0)	29 (3.9)	
15%	27 (17.8)	235 (31.9)		31 (20.4)	240 (32.6)	
25%	109 (71.7)	448 (60.8)	0.001	104 (68.4)	439 (59.6)	0.002
40%	10 (6.6)	25 (3.4)		12 (3.5)	26 (4.3)	
75%	2 (1.3)	2 (0.3)		2 (0.4)	3 (0.6)	
AOD250† (μm)	40.0 (71.5)	37.5 (74.5)	0.57	22.0 (78.0)	37.5 (71)	0.43
AOD500† (μm)	83.0 (81.5)	68.5 (80.0)	0.14	69.0 (71.5)	65.5 (77.0)	0.50
AOD750† (μm)	138.0 (108.5)	113.0 (98.5)	0.007	130.0 (95.0)	113.3 (86.0)	0.07
TISA500† (1000 μm^2)	35.5 (30.5)	32.5 (32.0)	0.41	29.5 (39.0)	32.0 (31.5)	0.90
TISA750† (1000 μm^2)	74.0 (54.5)	67.0 (59.0)	0.43	61.5 (59.0)	66.3 (54.5)	0.63
ARA† (1000 μm^2)	75.0 (72.5)	71.0 (67.5)	0.48	66.5 (62.0)	69.0 (61.0)	0.47

† PTM: posterior/pigmented trabecular meshwork; AOD: angle opening distance; TISA: trabecular-iris space area; ARA: angle recess area; § Chi square test for comparing proportions of eyes with different levels of van Herick scores, Mann-Whitney tests for other variable

Table 5 Quadrantal Analysis of Baseline Anatomical Features of Anterior Chamber Angle of PACS Eyes

	Treated Eyes [Median (Interquartile range)]					**Untreated Eyes** [Median (Interquartile range)]				
	Superior	**Nasal**	**Inferior**	**Temporal**	***P* value†**	**Superior**	**Nasal**	**Inferior**	**Temporal**	***P* value†**
Angle Width (°)§	7.7 (7.9)	16.8 (7.2)	16.6 (7.3)	14.3 (8.0)	<0.001	6.7 (7.1)	15.8 (7.5)	16.6 (6.9)	14.3 (8.4)	<0.001
				Spaeth Grades (N)						
A	77 (8.7)	110 (12.4)	522 (58.7)	185 (20.8)		84 (9.5)	116 (13.1)	507 (57.0)	178 (20.0)	
B	653 (73.5)	650 (73.1)	365 (40.1)	600 (67.5)	<0.001	645 (72.6)	633 (71.2)	378 (42.5)	604 (67.9)	<0.001
C	148 (16.7)	127 (14.3)	2 (0.2)	101 (11.4)		148 (16.7)	136 (15.3)	4 (0.5)	105 (11.8)	
D	11 (1.2)	2 (0.2)	0 (0.0)	3 (0.3)		12 (1.4)	4 (0.5)	0 (0.0)	2 (0.2)	
ITC (clockhour)§	1.7 (1.4)	0.4 (0.9)	0.4 (0.9)	0.7 (1.1)	<0.001	1.7 (1.4)	0.4 (1.0)	0.3 (0.9)	0.7 (1.2)	<0.001
AOD250‡ (μm)	0.0 (77.0)	80.0 (146.0)	36.0 (104.0)	112.0 (126.0)	<0.001	0.0 (76.0)	80.0 (147.0)	35.0 (82.0)	112.0 (122.0)	<0.001
AOD500‡ (μm)	41.0 (88.0)	112.0 (99.0)	84.0 (113.0)	123.0 (97.0)	<0.001	41.0 (85.0)	113.0 (101.0)	80.0 (141.0)	119.0 (94.0)	<0.001
AOD750‡ (μm)	83.0 (88.0)	149.0 (93.0)	145.0 (147.0)	166.0 (105.0)	<0.001	84.0 (88.0)	151.0 (94.0)	143.0 (117.0)	170.0 (107.0)	<0.001
TISA500‡ (1000 μm^2)	25.0 (38.0)	57.0 (51.0)	38.0 (42.0)	71.0 (47.0)	<0.001	25.0 (36.0)	59.0 (49.0)	33.0 (43.0)	71.0 (47.0)	<0.001
TISA750‡ (1000 μm^2)	53.0 (62.0)	104.0 (68.0)	73.0 (65.0)	116.0 (68.0)	<0.001	53.0 (59.0)	100.0 (72.0)	78.0 (73.0)	116.0 (63.0)	<0.001
ARA‡ (1000 μm^2)	54.0 (64.0)	113.0 (90.0)	75.0 (72.0)	131.0 (90.0)	<0.001	53.0 (65.0)	109.0 (93.0)	80.0 (79.0)	130.0 (85.0)	<0.001

† Kruskal-Wallis test was used for inter-quadrant comparisons; ‡ Number of eyes; PTM: posterior/pigmented trabecular meshwork; AOD: angle opening distance; TISA: trabecular-iris space area; ARA: angle recess area; ITC: iridotrabecular contact; § Data shown are means (standard deviations)

Table 6 Quadrantal Analysis of Baseline Anatomical Features of Anterior Chamber Angle of PACS‡ Eyes in Men

	Treated Eyes [Median (Interquartile range)]					Untreated Eyes [Median (Interquartile range)]				
	Superior	Nasal	Inferior	Temporal	P value†	Superior	Nasal	Inferior	Temporal	P value†
Angle Width (°)§	7.4 (7.3)	17.0 (7.6)	17.9 (7.1)	16.5 (8.1)	<0.001	8.4 (7.7)	17.3 (7.6)	17.2 (7.2)	16.8 (8.1)	<0.001
Spaeth Grades [N(95%)]										
A	85 (55.9)	14 (9.2)	14 (9.2)	17 (11.2)	<0.001	77 (50.7)	15 (9.9)	14 (9.2)	14 (9.2)	<0.001
B	67 (44.1)	107 (70.4)	109 (71.7)	106 (69.7)		74 (48.6)	107 (70.4)	107 (70.4)	103 (67.8)	
C	0 (0.0)	30 (19.7)	26 (17.1)	27 (17.8)		1 (0.7)	28 (18.4)	26 (17.1)	34 (22.4)	
D	0 (0.0)	1 (0.7)	3 (2.0)	2 (1.3)		0 (0.0)	2 (1.3)	5 (3.3)	1 (0.7)	
ITC (clockhour)§	1.6 (1.4)	0.3 (0.8)	0.3 (0.9)	0.5 (1.1)	<0.001	1.5 (1.4)	0.3 (0.9)	0.3 (0.9)	0.4 (1.0)	<0.001
AOD250‡ (μm)	0.0 (41.0)	75.0 (118.0)	43.0 (106.0)	103.0 (144.0)	<0.001	0.0 (78.0)	70.0 (136.0)	0.0 (112.0)	106.0 (144.0)	<0.001
AOD500‡ (μm)	41.0 (105.0)	81.0 (94.5)	109.0 (147.0)	111.0 (87.0)	<0.001	41.0 (89.0)	83.0 (115.0)	105.0 (113.0)	110.0 (82.0)	<0.001
AOD750‡ (μm)	94.0 (115.0)	115.0 (101.5)	172.0 (176.0)	150.0 (81.5)	<0.001	86.0 (91.0)	122.0 (111.0)	155.0 (116.0)	147.0 (84.0)	<0.001
TISA500‡ (1000 μm2)	23.0 (39.0)	53.0 (52.5)	44.0 (42.0)	63.5 (45.0)	<0.001	25.0 (32.0)	47.0 (56.0)	33.0 (45.0)	63.0 (42.0)	<0.001
TISA750‡ (1000 μm2)	48.0 (58.0)	91.0 (73.0)	86.0 (70.0)	102.0 (55.0)	<0.001	50.0 (59.0)	88.0 (78.0)	75.0 (67.0)	102.0 (59.0)	<0.001
ARA‡ (1000 μm2)	48.0 (69.0)	93.5 (93.0)	88.0 (84.0)	117.5 (84.0)	<0.001	53.0 (62.0)	96.0 (87.0)	75.0 (77.0)	115.0 (91.0)	<0.001

† Kruskal-Wallis test was used for inter-quadrant comparisons; ‡ Number of eyes; PTM: posterior/pigmented trabecular meshwork; AOD: angle opening distance; TISA: trabecular-iris space area; ARA: angle recess area; ITC: iridotrabecular contact; § Data shown are means (standard deviations), PACS: primary angle-closure suspect

Table 7 Quadrantal Analysis of Baseline Anatomical Features of Anterior Chamber Angle of PACS‡ Eyes in Women

	Treated Eyes [Median (Interquartile range)]					**Untreated Eyes** [Median (Interquartile range)]				
	Superior	**Nasal**	**Inferior**	**Temporal**	***P* value§**	**Superior**	**Nasal**	**Inferior**	**Temporal**	***P* value§**
Angle Width (°)	6.5 (6.8)	15.5 (7.1)	16.3 (7.3)	13.8 (7.9)	<0.001	6.4 (6.9)	15.5 (7.4)	16.5 (6.9)	13.8 (8.3)	<0.001
Spaeth Grades (N) †										
A	437 (59.3)	96 (13.0)	63 (8.6)	168 (22.8)		430 (58.3)	101 (13.7)	70 (9.5)	164 (22.3)	
B	298 (40.4)	543 (73.7)	544 (73.8)	494 (67.0)	<0.001	304 (41.3)	526 (71.4)	538 (73.0)	501 (68.0)	<0.001
C	2 (0.3)	97 (13.2)	122 (16.6)	74 (10.0)		3 (0.4)	108 (14.7)	122 (16.5)	71 (9.6)	
D	0 (0.0)	1 (0.1)	8 (1.1)	1 (0.1)		0 (0.0)	2 (0.3)	7 (1.0)	1 (0.1)	
ITC (clockhour) †	1.7 (1.4)	0.5 (0.9)	0.4 (0.9)	0.7 (1.1)	<0.001	1.8 (1.4)	0.5 (1.0)	0.4 (0.9)	0.8 (1.2)	<0.001
AOD250‡ (μm)	0.0 (79.0)	40.0 (116.0)	36.0 (104.0)	78.0 (141.0)	<0.001	0.0 (76.0)	42.0 (113.0)	35.0 (81.0)	76.0 (141.0)	<0.001
AOD500‡ (μm)	41.0 (87.0)	78.5 (120.0)	82.0 (111.0)	105.0 (104.0)	<0.001	40.0 (85.0)	77.0 (120.0)	77.5 (140.0)	90.0 (100.0)	<0.001
AOD750‡ (μm)	83.0 (88.0)	115.0 (84.0)	143.0 (141.0)	138.0 (105.0)	<0.001	83.0 (88.0)	114.0 (87.0)	141.0 (117.0)	126.0 (104.0)	<0.001
TISA500‡ (1000 μm2)	26.0 (37.0)	42.0 (50.0)	36.0 (44.0)	58.0 (48.0)	<0.001	24.5 (36.0)	44.0 (48.0)	33.0 (42.0)	55.0 (50.0)	<0.001
TISA750‡ (1000 μm2)	53.0 (59.0)	77.5 (65.0)	75.0 (69.0)	95.0 (61.0)	<0.001	53.0 (61.0)	81.0 (70.0)	73.0 (65.0)	92.0 (65.0)	<0.001
ARA‡ (1000 μm2)	55.0 (63.0)	80.0 (81.0)	78.0 (78.0)	103.0 (78.0)	<0.001	54.0 (65.0)	85.0 (85.0)	74.0 (71.0)	101.0 (87.0)	<0.001

† Number of eyes, ITC: irido-trabecular contact; § Kruskal-Wallis test was used for inter-quadrant comparisons; Chi square tests for comparing proportions

‡ PACS: primary angle-closure suspect, PTM: posterior/pigmented trabecular meshwork; AOD: angle opening distance; TISA: trabecular-iris space area; ARA: angle recess area

Table 8 Weight, Height, BMI and Mean Angle Width

Quartile Groups	Mean angle width† [n (%)]			Total [n (%)]
	0~10°	15°~25°	≥30°	
Weight (kg)				
≥27 and <50	55(40.74)	57(33.53)	124(20.84)	236 (26.22)
≥50 and <57	39(28.89)	43(25.29)	141(23.70)	223 (24.78)
≥57 and <64	26(19.26)	41(24.12)	167(28.07)	234 (26.00)
≥64 and <94	15(11.11)	29(17.06)	163(27.39)	207 (23.00)
Tests for trend across ordered groups: z=6.38, P<0.001				
Height (m)				
≥1.18 and <1.50	58(42.96)	70(41.18)	123(20.67)	251 (27.89)
≥1.50 and <1.55	37(27.41)	37(21.76)	135(22.69)	209 (23.22)
≥1.55 and <1.62	27(20.00)	36(21.18)	165(27.73)	228 (25.33)
≥1.62 and <1.81	13(9.63)	27(15.88)	172(28.91)	212 (23.56)
Tests for trend across ordered groups: z=7.62, P<0.001				
BMI (kg/m2)				
≥14.79 and <21.34	47(34.81)	42(24.71)	136(22.86)	225 (25.00)
≥21.34 and <23.51	38(28.15)	40(23.53)	148(24.87)	226 (25.11)
≥23.51 and <25.78	24(17.78)	44(25.88)	158(26.55)	226 (25.11)
25.78 ~ 35.82	26(19.26)	44(25.88)	153(25.71)	223 (24.78)
Tests for trend across ordered groups: z=2.50, P<0.01				
Total	135(100.00)	170(100.00)	595(100.00)	900 (100.00)

†mean angle width: calculated from mean Shaffer grade of the superior and inferior quadrant; Shaffer grade was missing in 12 subjects

Table 9 Association of Narrow Angle† with Anthropomorphic Measures and Other Factors (Univariate Logistic Regression Models)

	Narrow Angle†		
	OR	**95% CI**	**P value**
Age, per decade	2.12	(1.69, 2.67)	<0.001
Sex Male		Reference category	
Female	2.05	(1.29, 3.24)	0.002
Weight, per 10Kg	0.53	(0.42, 0.67)	<0.001
Height, per 10cm	0.55	(0.43, 0.71)	<0.001
BMI (Kg/m2)	0.89	(0.83, 0.95)	0.001
Axial length (mm)	0.45	(0.34, 0.58)	<0.001
Anterior chamber depth (mm)	0.02	(0.01, 0.05)	<0.001
Spherical equivalent (Dioptres)	1.27	(1.10, 1.46)	0.001
Education level			
No formal or primary		Reference category	
Middle or college	0.39	(0.25, 0.61)	<0.001
Occupation§	1.09	(0.93, 1.28)	0.29
Income§	0.69	(0.47, 1.02)	0.07

† Narrow angle was defined as pigmented trabecular meshwork not visible in at least 3 quadrants under static gonioscopy; § Occupation categories include: household, unemployed, unskilled manual worker, skilled manual worker, cleric/manager, semi-professional, professional; income categories: monthly income RMB<1000, ≧1000/<3000, ≧3000/<7000, ≧7000/<10,000, ≧10,000/15,000, ≧15,000

Table 10 Association between Narrow Angle and BMI (Multiple Logistic Regression Model)

	Narrow Angle†		
	OR	**95% CI**	***P* value**
Age per decade	2.01	(1.49, 2.71)	<0.001
Sex			
Male		Reference category	
Female	1.28	(0.63, 2.62)	0.50
BMI (Kg/m^2)	0.93	(0.86, 0.99)	0.026
Height, per 10cm	0.99	(0.64, 1.54)	0.97
Education level			
No formal or primary		Reference category	
Middle or college	0.90	(0.51, 1.58)	0.72
Axial length (mm)	0.59	(0.42, 0.81)	0.001
ACD§ (mm)	0.05	(0.02, 0.17)	<0.001

† Narrow angle was defined as pigmented trabecular meshwork not visible in at least 3 quadrants under static gonioscopy; § ACD: central anterior chamber depth

Table 11 Association between Narrow Angle and Body Height (Logistic Regression Models)

	Narrow Angle†		
	OR	**95% CI**	P value
Crude data			
Height, per 10 cm	0.55	(0.43, 0.71)	<0.001
Adjusted for sex			
Height, per 10 cm	0.57	(0.41, 0.79)	0.001
Sex	1.08	(0.60, 1.94)	0.808
Adjusted for age			
Height, per 10 cm	0.69	(0.52, 0.90)	0.006
age	1.07	(1.04, 1.09)	<0.001
Adjusted for age and sex			
Height, per 10 cm	0.87	(0.59, 1.26)	0.455
sex	1.77	(0.93, 3.36)	0.080
age	1.07	(1.05, 1.10)	<0.001
Adjusted for axial length and ACD*			
Height, per 10 cm	0.67	(0.50, 0.89)	0.006
Axial length (mm)	0.74	(0.56, 0.99)	0.039
ACD (mm)	0.03	(0.01, 0.09)	<0.001
Adjusted for axial length, ACD, sex and age			
Height, per 10 cm	1.00	(0.65, 1.54)	0.999
Sex	1.37	(0.69, 2.74)	0.371
Age	1.08	(1.05, 1.11)	<0.001
Axial length (mm)	0.60	(0.43, 0.83)	0.002
ACD (mm)	0.05	(0.02, 0.14)	<0.001

† Narrow angle was defined as pigmented trabecular meshwork not visible in at least 3 quadrants under static gonioscopy.

Table 12 Association between BMI and Narrow Angle (Multiple Logistic Regression Analysis Stratified by Sex)

	Narrow Angle†		
Males	**OR**	**95% CI**	**P value**
Age, per decade	2.71	(1.58, 4.63)	<0.001
BMI (Kg/m2)	0.97	(0.85, 1.11)	0.629
Height, per 10cm	0.92	(0.42, 1.99)	0.83
Education level			
No formal or primary		Reference category	
Middle or college	1.81	(0.66, 4.95)	0.25
Axial length (mm)	0.38	(0.20, 0.73)	0.004
Anterior chamber depth (mm)	0.14	(0.03, 0.80)	0.027
Females			
Age, per decade	1.77	(1.23, 2.56)	0.002
BMI (Kg/m2)	0.90	(0.83, 0.98)	0.014
Height, per 10cm	1.04	(0.61, 1.79)	0.88
Education level			
No formal or primary		Reference category	
Middle or college	0.62	(0.30, 1.29)	0.20
Axial length (mm)	0.67	(0.46, 0.98)	0.038
Anterior chamber depth (mm)	0.04	(0.01, 0.16)	<0.001

† Narrow angle was defined as pigmented trabecular meshwork not visible in at least 3 quadrants under static gonioscopy

Table 13 Associations of Angle Width of Male Primary Angle-closure Suspects in the ZAP Trial (Univariate Analysis‡)

	Regression Coeffients (R-squares (%))						
	Angle Width (°)	**AOD250 (μm)**	**AOD500 (μm)**	**AOD750 (μm)**	**TISA500 (1000 μm2)**	**TISA750 (1000 μm2)**	**ARA (1000 μm^2)**
Age	0.10 (0.70)	-0.13 (0.02)	-0.97 (0.69)	-0.83 (0.28)	-0.04 (<0.01)	-1.72 (2.30)	-1.67 (1.67)
Height (m)	0.23* (5.41)	-1.06 (2.18)	-1.00 (1.12)	-1.21 (0.89)	-0.56 (1.72)	-1.5 (2.89)	-1.48 (1.97)
Weight (kg)	0.13* (4.44)	0.07 (0.02)	0.13 (0.05)	0.34 (0.18)	0.07 (0.07)	-0.01 (<0.01)	0.05 (<0.01)
BMI† (kg/m^2)	0.24 (1.44)	1.54 (1.08)	1.82 (0.87)	2.92 (1.21)	0.99 (1.29)	1.96 (1.05)	2.13 (0.96)
ACD† (mm)	6.83* (4.55)	42.55 (3.29)	80.07** (6.77)	154.10** (0.14)	17.80 (1.66)	23.81 (0.63)	29.72 (0.75)
Axial Length (mm)	1.25 (1.88)	-4.99 (0.56)	3.89 (0.20)	6.17 (0.27)	-5.73 (0.21)	-10.98 (1.64)	-11.22 (1.32)
Lens Thickness (mm)	-3.94* (4.29)	1.88 (0.02)	-4.32 (0.06)	-33.78 (1.84)	0.94 (0.01)	-16.64 (0.87)	-19.02 (0.87)
Occupation§	0.19 (5.82)	-1.91 (1.05)	-2.71 (1.23)	-2.89 (7.51)	-2.00 (3.31)	-6.18** (6.70)	-6.19* (5.18)
House Space	-0.01 (0.07)	-0.04 (0.11)	-0.11 (4.39)	-0.27 (1.39)	-0.03 (1.48)	0.02 (<0.01)	-0.004 (<0.01)
Education§	0.89 (1.46)	1.25 (0.05)	6.72 (0.91)	4.09 (0.18)	3.26 (1.06)	4.24 (0.38	4.01 (0.26)
Income (¥)§	0.75 (2.28)	-1.22 (0.11)	-5.78 (1.47)	-9.50 (2.13)	-1.69 (0.62)	-3.81 (0.67)	-5.49 (1.07)

† AOD: angle opening distance; TISA: trabecular-iris space area; ARA: angle recess area; ACD: central anterior chamber depth; BMI: body mass index; ‡ Univariate Linear Regression Models,Treated Eyes; §Occupation categories include: household, unemployed, unskilled manual worker, skilled manual worker, cleric/manager, semi-professional, professional; income categories: monthly income categories (unit: Yuan): <1000, ≧1000/<3000, ≧3000/<7000, ≧7000/<10,000, ≧10,000/15,000, ≧15,000; education categories: no formal education; primary school; secondary/technical school; pre-university/polytechnical school; college/university ** p<0.01, * p<0.05

Table 14 Associations of Angle Width of Male Primary Angle-closure Suspects in the ZAP Trial (Multiple Liner Regression‡)

	Regression Coefficients						
	Angle Width (°)	AOD250 (μm)	AOD500 (μm)	AOD750 (μm)	TISA500 (1000 μm2)	TISA750 (1000 μm2)	ARA (1000 μm2)
Age	0.14	-0.19	-1.02	-0.34	0.14	-1.35	-1.14
Height (m)	0.20*	-1.27	-1.16	-1.34	-0.63	-1.72	-1.59
BMI† (kg/m2)	0.07	1.64	2.04	2.70	1.28	2.87	3.05
ACD† (mm)	4.45	67.93**	95.06**	165.17**	32.79*	40.89	45.41
Axial Length (mm)	0.36	-13.43	-6.34	-14.90	-10.67*	-18.46*	-19.65
Lens Thickness (mm)	-3.09	13.22	21.58	3.08	6.44	-9.84	-11.54
Occupation§	0.25	-2.18	-2.48	-3.52	-2.22**	-6.79**	-6.93*
House Space	-0.01	-0.02	-0.04	-0.07	-0.03	0.04	0.05
Education§	0.79	2.08	9.25	6.43	3.49	1.44	1.24
Income (¥)§	0.72	0.72	-4.02	-6.62	-1.62	-2.54	-4.22
R-square (%)	17.8	12.0	14.0	19.0	16.2	18.8	15.3

† AOD: angle opening distance; TISA: trabecular-iris space area; ARA: angle recess area; ACD: central anterior chamber depth; BMI: body mass index; ‡ Multiple Linear Regression Models,Treated Eyes; §Occupation categories include: household, unemployed, unskilled manual worker, skilled manual worker, cleric/manager, semi-professional, professional; income categories: monthly income categories (unit: Yuan): <1000, ≧1000/<3000, ≧3000/<7000, ≧7000/<10,000, ≧10,000/15,000, ≧15,000; education categories: no formal education; primary school; secondary/technical school; pre-university/polytechnical school; college/university ** p<0.01, * p<0.

Table 15 Associations of Angle Width of Female Primary Angle-closure Suspects in the ZAP Trial (Univariate Analysis‡)

	Regression Coeffients (R-squares (%))						
	Angle Width (°)	AOD250 (μm)	AOD500 (μm)	AOD750 (μm)	TISA500 (1000 μm2)	TISA750 (1000 μm2)	ARA (1000 μm2)
Age	-0.02 (0.02)	0.87 (0.69)	0.34 (0.07)	0.08 (<0.01)	0.61* (1.17)	0.66 (0.18)	1.19 (0.38)
Height (m)	0.10* (0.89)	-0.12 (0.02)	-0.33 (0.09)	0.08 (<0.01)	-0.28 (0.33)	-0.83 (0.37)	-1.02 (0.36)
Weight (kg)	0.05 (0.50)	0.39 (0.48)	0.54 (0.65)	1.16** (1.76)	0.18 (0.35)	0.38 (0.21)	0.50 (0.24)
BMI† (kg/m2)	0.05 (0.09)	1.18 (0.70)	1.76* (1.11)	3.11** (0.02)	0.70* (0.85)	1.68 (0.64)	2.10 (0.65)
ACD† (mm)	6.14** (5.17)	26.64* (1.17)	76.00** (7.91)	128.31** (13.1)	19.23** (2.49)	27.46 (0.66)	36.81* (0.77)
Axial Length (mm)	1.14** (1.84)	3.02 (0.18)	7.81* (0.86)	14.22** (1.65)	1.74 (0.21)	3.70 (0.12)	4.93 (0.14)
Lens Thickness (mm)	-2.75** (1.96)	-9.10 (0.33)	-30.37** (2.39)	-45.26** (3.08)	-7.12 (0.65)	-19.94 (0.66)	-27.65* (0.82)
Occupation§	0.01 (<0.01)	-1.62* (0.76)	-2.52** (1.31)	-3.73** (1.66)	-0.55 (0.31)	-1.59 (0.33)	-1.43 (0.17)
House Space	0.01 (0.06)	0.07 (0.15)	0.17 (0.65)	0.44** (0.02)	0.02 (0.05)	-0.08 (0.08)	-0.08 (0.05)
Education§	0.04 (<0.01)	1.00 (0.04)	2.44 (0.17)	5.66 (0.52)	-0.25 (<0.01)	-1.79 (0.06)	-1.19 (0.02)
Income (¥)§	0.03 (<0.01)	0.17 (<0.01)	2.40 (0.23)	7.76** (1.37)	0.28 (0.01)	-0.16 (<0.01)	-0.05 (<0.01)

† AOD: angle opening distance; TISA: trabecular-iris space area; ARA: angle recess area; ACD: central anterior chamber depth; BMI: body mass index; ‡ Univariate Linear Regression Models,Treated Eyes; §Occupation categories include: household, unemployed, unskilled manual worker, skilled manual worker, cleric/manager, semi-professional, professional; income categories: monthly income categories (unit: Yuan): <1000, ≧1000/<3000, ≧3000/<7000, ≧7000/<10,000, ≧10,000/15,000, ≧15,000; education categories: no formal education; primary school; secondary/technical school; pre-university/poly-technical school; college/university ** p<0.01, * p<0.05

Table 16 Associations of Angle Width of Female Primary Angle-closure Suspects in the ZAP Trial (Multiple Liner Regression‡)

	Regression Coefficients						
	Angle Width (°)	**AOD250 (μm)**	**AOD500 (μm)**	**AOD750 (μm)**	**TISA500 (1000 μm2)**	**TISA750 (1000 μm2)**	**ARA (1000 μm2)**
Age	0.02	1.15*	0.63	0.41	0.72**	0.79	1.56
Height (m)	0.10*	0.04	-0.36	-0.16	-0.16	-0.60	-0.68
BMI† (kg/m2)	0.04	1.25*	1.53*	2.65**	0.62	1.57	1.96
ACD† (mm)	5.10**	21.94	71.99**	125.02**	18.68**	13.84	18.36
Axial Length (mm)	0.38	-1.57	-3.05	-4.72	-1.37	0.93	0.68
Lens Thickness (mm)	-0.88	-4.71	-6.11	0.84	-3.13	-17.16	-25.70
Occupation§	0.04	-1.60	-2.24*	-3.02*	-0.55	-1.90	-1.61
House Space	-0.00	0.05	0.13	0.31*	0.01	-0.08	-0.10
Education§	-0.04	1.69	1.34	2.19	0.52	-1.12	0.80
Income (¥)§	-0.15	-2.00	-1.66	0.32	-0.65	-0.65	-1.13
R-square (%)	6.41	3.67	10.40	17.20	5.19	2.57	2.78

† AOD: angle opening distance; TISA: trabecular-iris space area; ARA: angle recess area; ACD: central anterior chamber depth; BMI: body mass index; ‡ Multiple Linear Regression Models,Treated Eyes; §Occupation categories include: household, unemployed, unskilled manual worker, skilled manual worker, cleric/manager, semi-professional, professional; income categories: monthly income categories (unit: Yuan): <1000, ≧1000/<3000, ≧3000/<7000, ≧7000/<10,000, ≧10,000/15,000, ≧15,000; education categories: no formal education; primary school; secondary/technical school; pre-university/polytechnical school; college/university ** p<0.01, * p<0.05

6. Qualitative Assessment of Anatomical Features of Eyes with Remained Narrow Angle Following LPI

6.1. Introduction

The configuration of anterior chamber angle is largely determined by structures that surround or shape the drainage angle, such as the iris and the ciliary body. For example, the iris, being the structure that defines the posterior border of the anterior chamber angle, can affect the drainage angle configuration by the contour of its anterior surface, the bulk of its peripheral portion, and the location where it inserts onto the corneoscleral wall.

In a previous study of relatively smaller sample size on PACS eyes of elderly Chinese, He et al [232] reported that up to 19.4% of PACS eyes remained to have narrow angles (see 5.2.4 for the definition) after LPI. In other words, the narrow angle configuration in one out of five PACS eyes may result from mixed mechanism including non-pupillary block factors , as creation of a bypass route for aqueous flow between the posterior and anterior chamber could not resolve the narrow angle condition. Then what are the anatomical features leading to persistent narrow angle configurations after the elimination of pupillary block? Are there any possible ways to predict the outcomes of

LPI by assessing some simple qualitative features in scans from anterior segment imaging devices?

UBM has been proven to be a great asset in research and clinical assessment of angle-related structures. Radially-orientated scanning through the limbus provides a cross-sectional view of the drainage angles with near-microscopic lateral and axial resolution [233]. Examples of UBM's application in the field of anterior chamber angle assessment include detection or confirmation of appositional angle closure, verification of ciliary process position and identification of other abnormalities related to the drainage angle and ciliary body [232]. One great merit of UBM lies in its ability to reveal characteristics of some angle-related structures posterior to the iris that are otherwise hidden from clinical observation. Visualisation of these structures may help achieve insight into causative factors underlying various angle configurations. Gonioscopy is currently regarded as the reference standard for clinical assessment of the anterior chamber angle. However, it is a technically demanding examination that depends on the examiner's subjective judgment. A significant weakness of the technique is that it cannot provide definitive information on anatomy of structures posterior to the iris which may influence angle width. Although AS-OCT has proved to be a simple, non-contact alternative for the imaging of drainage angle, the iris pigment epithelium limits infra-red radiation transmission and thus may limit visualisation of structures posterior to the iris [85,234,235] .

In the current analysis, using a qualitative grading system [84] , UBM images of eyes with residual narrow angles were compared to eyes with wide open drainage angles, after LPI. Images were qualitatively assessed for iris thickness, level of iris insertion, iris profile and iris curvature, and the size and position of ciliary processes.

6.2. Methods

6.2.1. Definitions & Study Subjects

Based on findings of static gonioscopy at 18 months following LPI, eyes with PTM not visible in 3 or more quadrants under static gonioscopy (i.e. a circumference of at least 270º) were defined as eyes with persistent narrow angle after LPI. In contrast, those with PTM visible in all 4 quadrants under static gonioscopy at 18 months post-LPI were defined as eyes with wide open angle after LPI. UBM scans of the superior and temporal quadrants were selected from 99 eyes randomly selected from 151 eyes with persistent narrow angles after LPI in the ZAP study cohort and 92 control eyes randomly selected from 308 eyes with wide open angle after LPI.

6.2.2. UBM Examination

See 3.1.3.2 for a description of the method used for UBM scanning. The probe was always oriented perpendicular to the ocular surface. To reveal the relationship between

the iris and the ciliary body, care was taken to ensure the radial perpendicular UBM scans be obtained through a typical ciliary process. The gain was set to between 60 to 80 dB in order to have a clear display on the structure and minimise the ultrasound noise simultaneously. The criteria for acceptable images were: clear visualisation of the scleral spur, angle, ciliary body and a half chord of the iris. The tangent line of the anterior surface of the lens should ideally be horizontal in order to ensure standardisation of the layouts of the images.

6.2.3. Qualitative Grading of UBM Images Using Standard Photos

All UBM images were qualitatively graded by comparison with a set of standard photos for the assessment of the following features: 1) Iris thickness: the overall thickness and the thickness of peripheral 1/3 of the iris (termed basal iris thickness) were graded relative to the limbal corneal thickness (**Figure 9**); 2) Iris curvature: judged by the curvature of the posterior surface of the iris. (**Figure 10**); 3) Iris insertion: graded according to the location of the iris insertion on the ciliary body (

Figure 11); 4) Iris angulation: identified if the iris had to make an abrupt change in the direction at its insertion to ciliary body (

Figure 11); 5) Ciliary body size: identified as the greatest distance in a straight line between the apex of the ciliary body and base, as close as possible to a perpendicular position from the sclera, in reference to the limbal cornea thickness: small – less than limbal corneal thickness, medium – 1~1.99 limbal corneal distance; large - >= 2 limbal

corneal thickness (

Figure 12) 6) Ciliary process position: classified as neutral or anteriorly positioned based on the direction of the axis of ciliary body (

Figure 12)

6.2.4. Statistical Analysis

Anatomical features of eyes with and without residual angle-closure after LPI were compared using Chi square tests. All statistical analyses were performed using Stata/SE 13.1 (StataCorp, College Station, TX, USA). A *P* value of 0.05 or lower was considered statistically significant.

6.3. Results

Table **17** summarises the baseline anatomical features of angle-related structures in eyes with narrow and wide angles at 18 months following LPI. Comparing the superior and temporal quadrant, a significantly higher proportion of eyes had basal iris insertion in the superior quadrant (P<0.01). No other significant inter-quadrant difference was found in anatomical features of angle-related structures between the superior and temporal quadrant in both eyes with narrow angles and those with wide open angles

after LPI.

As shown in **Figure 5** to **Figure 7** and **Table 17 Qualitative Analysis of Baseline Anatomical Features of Eyes with Narrow and Wide Angles at 18 Months after LPI**, in the current analysis, compared to eyes with wide open angles after LPI, a significantly greater proportion of eyes with persistent narrow angles after LPI had medium or thick overall iris thickness. The proportion of eyes with medium or thick basal iris thickness is also significantly greater in eyes with residual narrow angle after LPI. A remarkably higher proportion of eyes with residual narrow angle after LPI had basal iris insertion, especially in the superior quadrant. Eyes with wide open angles after LPI tended to have neutral ciliary process, whereas those with residual angle narrowing after LPI tended to have anteriorly positioned ciliary process. The inter-group differences were significant in both the superior and temporal quadrants.

6.4. Discussion

Heretofore, there has not been adequate evidence for selecting the “perfect timing” for carrying out treatment intervention in patients with narrow angle configuration evident on examinations but without clinically manifest glaucomatous pathologies. Clinicians’ decisions for performing LPI by and large rely on the predicted clinical outcomes. It is however difficult for clinicians to tell which eyes will end up having immediately widened drainage angles which will be persistently open in the long run, and which

eyes will respond poorly to LPI and be in need of other intervention. For the latter category, a relatively better evidence-based prediction of the treatment results might help patients avoid undergoing treatment with poor efficacy and directly go for other potentially more effective alternatives such as argon laser iridoplasty [236] and lens extraction [237,238] .

In the current analysis, compared to eyes with wide-open angles after LPI, eyes with persistent narrow or occludable angles after LPI were found to have a thicker iris overall, a relatively more bulky peripheral iris, a more anteriorly inserted iris, and more anteriorly-positioned ciliary processes.

The results of this qualitative analysis are in accordance with findings of a previous quantitative study of smaller sample size in PACS eyes of elderly Chinese. Using quantitative measurements (i.e. angle opening distance, iris thickness, iris curvature, iris-ciliary process distance, and trabecular-ciliary process distance), He and colleagues [232] analysed UBM images and reported the following anatomical features of 14 PACS eyes with residual narrow angles after LPI (out of 72 eyes treated): smaller angle opening distance, thicker iris and more anteriorly positioned ciliary body. These eyes were also reported to have relatively more anteriorly inserted iris, although the difference was of borderline statistical significance between eyes with “closed” and “open” angles following LPI. There has also been study reporting a prevalence of plateau iris in at least one quadrant up to 32.3% in PACS eyes and 32.4% in eyes with

PACG after LPI. [239,240] These eyes were characterised by the presence of an anteriorly positioned ciliary body, an absent ciliary sulcus, a steep iris root from the insertion spot followed by a downward angulation from the corneoscleral wall and iridotrabecular contact. [239]

In this research, based on results reported in 5.3, the superior quadrant was selected out of all four quadrants to represent the relatively narrowest portion of the drainage angle in each eye. Using angle opening distance (i.e. AOD500) measured from UBM images, Gazzard found significantly greater angle width in the temporal quadrant, compared to the nasal and inferior quadrants (unpublished data, personal correspondence with Gus Gazzard), which is in accordance with findings in the current project (see 5.3.2 for details). Hence, scans of the temporal quadrants were also analysed for the purpose of inter-quadrant comparison with the superior quadrants. As shown in **Table 17 Qualitative Analysis of Baseline Anatomical Features of Eyes with Narrow and Wide Angles at 18 Months after LPI**, the only statistically significant difference lay in the location of iris insertion. Compared to the temporal quadrant, significantly higher proportions of eyes had a basal iris insertion (i.e. the most anterior/peripheral grade for the location of iris insertion). This may suggest that the location of iris insertion, among all anatomical features of angle-related structures, plays a relatively more important role in leading to poor outcomes of LPI in PACS eyes. Differing from findings of a previous study by the author [84] , the size and position of the ciliary process was not found to differ significantly between the superior and temporal quadrants.

Large, anteriorly positioned ciliary processes have been associated with plateau iris or the non-pupil block mechanisms of angle-closure in some previous studies [239,241] . In the current study, the majority of eyes with both narrow and wide open angles (79.8%-91.1%) after LPI were found to have medium size of the ciliary body. No statistically significant differences were found between ciliary body sizes in eyes with narrow or wide angle following LPI. The position of ciliary process, however, was found to be significantly different between the two groups. Compared to eyes with wide open angles following LPI, a significantly higher proportion of eyes with residual narrow angles after LPI had anteriorly positioned ciliary process. This may suggest a more important role of anteriorly positioned ciliary body/process position in shaping narrow angles after LPI, compared to the effect from large ciliary body size.

Results of the current research were in good accordance with findings of previous quantitative study. This gives further evidence for the validity of qualitative assessment using UBM images.[84]

Based on these study findings, it might be reasonable to assume that neither of the two ciliary body features alone is adequate to cause narrow angle configuration. Even the coexistence of both large and anteriorly-positioned ciliary processes is not a unique characteristic of narrow angle eyes with plateau iris configuration.[84] It is possible that only in combination with features of other angle-related anatomical structures such as

anterior iris insertion, thick peripheral iris and moderate or pronounced iris angulation, can the large anteriorly positioned ciliary body result in a narrow angle. Caution is also warranted in the interpretation of study outcomes in relate to sizes of the ciliary processes, as the cross-sectional area is used as a surrogate variable for quantifying volume of the ciliary body. It is not too difficult to imagine how this measurement method could be potentially inaccurate. Therefore when intending to identify the existence of plateau iris configuration or non-pupil block mechanisms of angle-closure, it might be more sensible to employ more comprehensive consideration of a combinative series of anatomical features including iridotrabecular contact, iris profile and thickness, as well as the bulk and position of the ciliary body. Results of the current research may help highlight some of the most predictive features out of this series, i.e. overall and peripheral thickness of the iris, location of iris insertion, and anatomical position of the ciliary body. This may be potentially useful for clinicians to quickly estimate the treatment outcomes of LPI by quickly assessing the above key qualitative features in UBM scans.

It would be even more helpful if a risk prediction algorithm could be developed based on easy qualitative assessment or automated quantitative grading of the UBM scans. Development of such a risk prediction algorithm would rely on qualitative and quantitative grading of larger sample size of PACS eyes with persistent narrow angle configurations following LPI.

Table 17 Qualitative Analysis of Baseline Anatomical Features of Eyes with Narrow and Wide Angles at 18 Months after LPI

	Superior Quadrant [N (%)]			Temporal Quadrant [N (%)]		
	Narrow angle eyes§	Wide angle eye§	*P* value	Narrow angle eyes§	Wide angle eye§	*P* value
Overall Iris Thickness						
Thin	2 (2.0)	10 (10.9)		3 (3.0)	13 (14.4)	
Medium	74 (74.8)	71 (77.2)	*0.009*	79 (79.8)	70 (77.8)	*0.005*
Thick	23 (23.2)	11 (12.0)		17 (17.2)	7 (7.8)	
Basal Iris Thickness						
Thin	4 (4.0)	26 (28.3)		7 (7.1)	35 (38.9)	
Medium	86 (86.9)	66 (71.7)	*<0.001*	88 (88.9)	54 (60.0)	*<0.001*
Thick	9 (9.1)	0 (0.0)		4 (4.0)	1 (1.1)	
Locations of Iris Insertion						
Basal	78 (78.8)	49 (53.3)		48 (48.5)	23 (25.6)	
Middle	21 (21.2)	37 (40.2)	<0.001	51 (51.5)	59 (65.6)	0.001
Apical	0 (0.0)	6 (6.5)		0 (0.0)	8 (8.9)	
Iris Angulation						
None	93 (93.9)	93 (93.9)		86 (86.8)	78 (86.7)	
Mild	3 (3.0)	3 (3.0)	0.095	12 (13.3)	12 (13.3)	0.056
Pronounced	3 (3.0)	3 (3.0)		0 (0.0)	0 (0.0)	
Size of Ciliary Body						
Small	12 (13.0)	14 (14.1)		4 (4.4)	6 (6.1)	
Medium	77 (83.7)	79 (79.8)	0.63	82 (91.1)	85 (85.9)	0.51
Large	3 (3.3)	6 (6.1)		4 (4.4)	8 (8.1)	
Position of Ciliary Body						
Neutral	35 (35.4)	57 (57.6)	0.002	66 (66.7)	38 (38.4)	<0.001
Anterior	64 (64.7)	42 (42.4)		33 (33.3)	61 (61.62)	

† LPI: laser peripheral iridotomy. § Data available in superior quadrant of 92 wide angle eyes and in temporal quadrant of 90 wide angle eyes; § Narrow angle eyes were defined as eyes in which the posterior trabecular meshwork was not visible in at least 3 quadrants under static gonioscopy following laser peripheral iridotomy; wide angle eyes were defined as eyes in which the posterior trabecular meshwork was visible under static gonioscopy in all 4 quadrants following laser peripheral iridotomy.

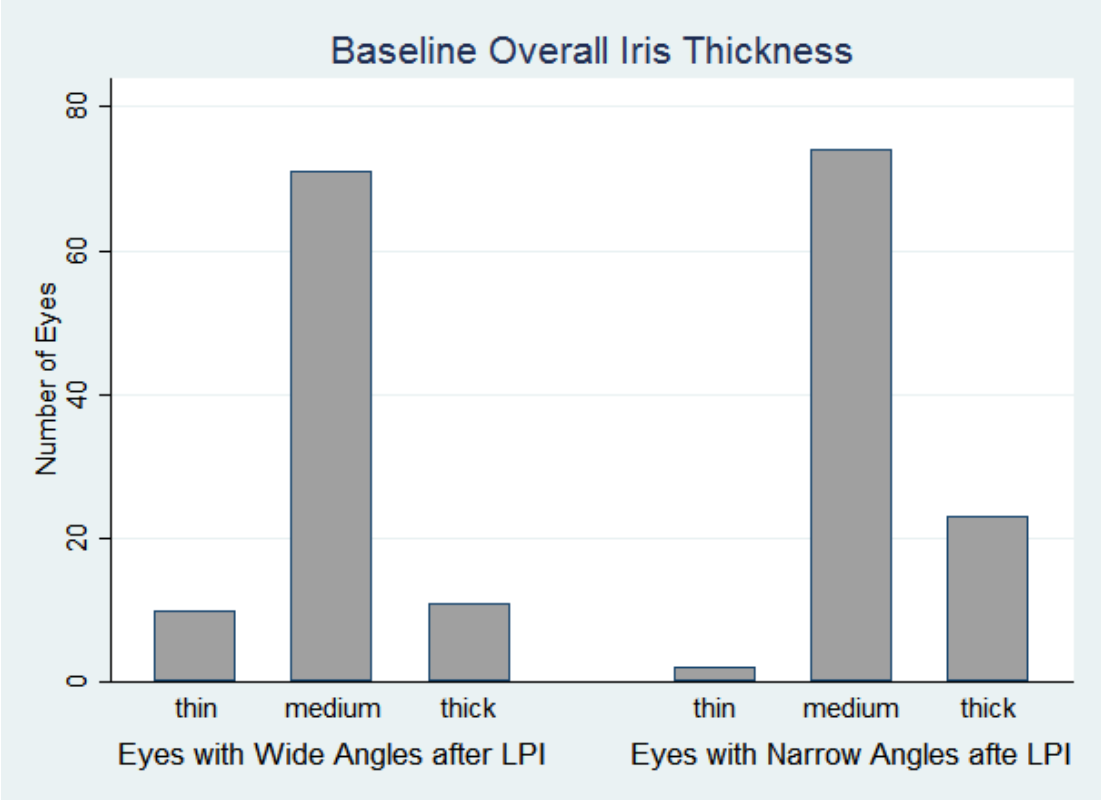


Figure 5 Comparison of Overall Iris Thickness between Eyes with Narrow or Wide Angles after LPI (Superior)

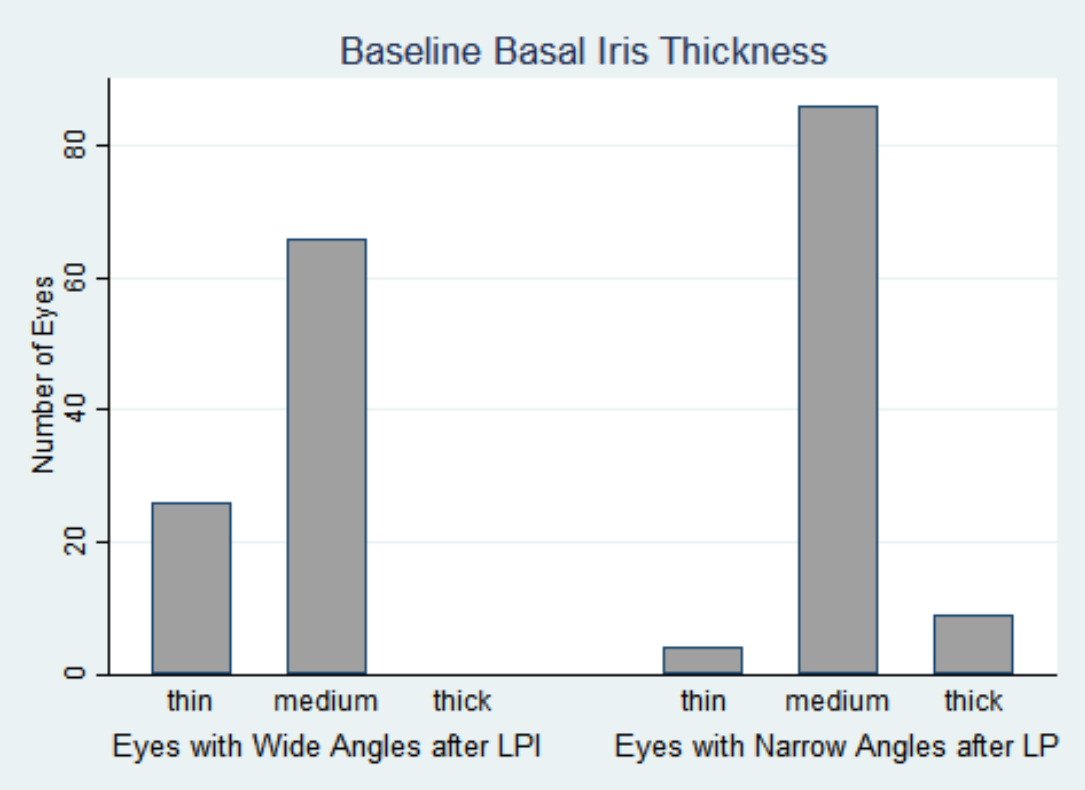


Figure 6 Comparison of Basal Iris Thickness between Eyes with Narrow or Wide Angles after LPI (Superior)

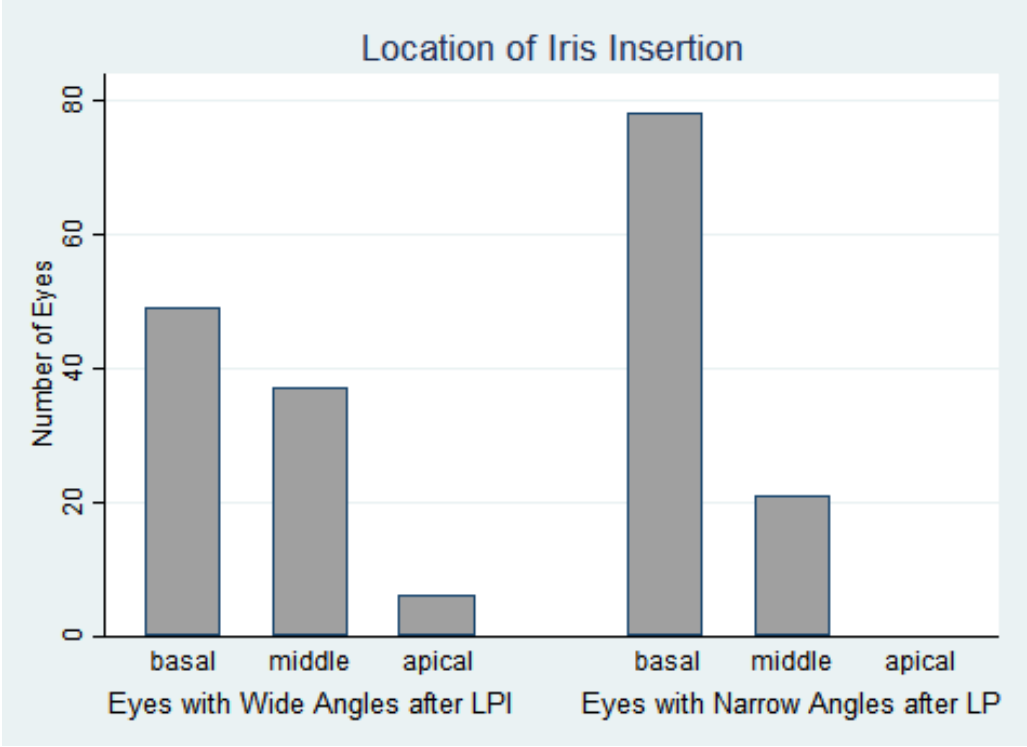


Figure 7 Comparison of Locations of Iris Insertion between Eyes with Narrow or Wide Angles after LPI (Superior)

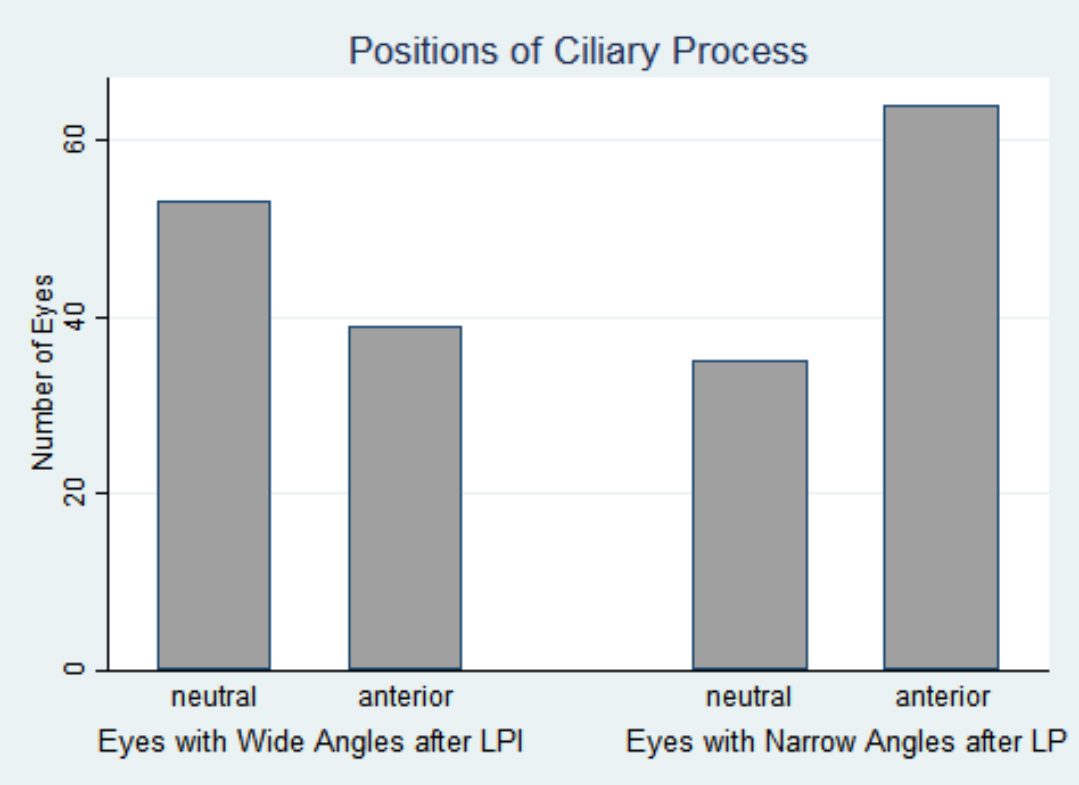


Figure 8 Comparison of Positions of Ciliary Process between Eyes with Narrow or Wide Angles after LPI

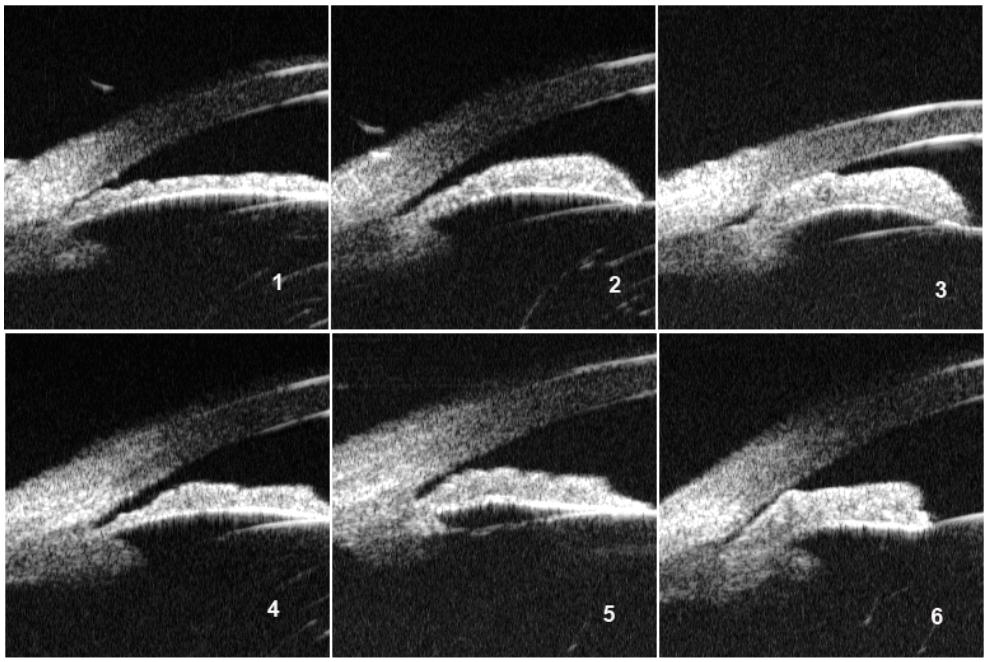


Figure 9 Standard photos used for assessing iris thickness. Referring to the limbal corneal thickness: 1. thin overall iris thickness; 2. medium overall iris thickness; 3. thick overall iris thickness; 4. thin basal iris thickness; 5. medium basal iris thickness; 6. thick basal iris thickness.

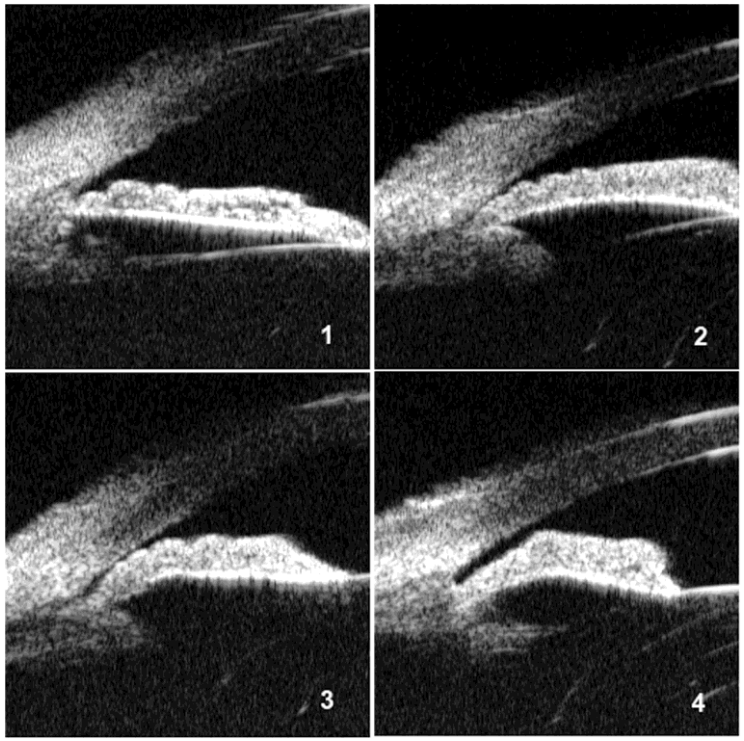


Figure 10 Iris curvature: 1. absent; 2. mild; 3. moderate; 4. extreme.

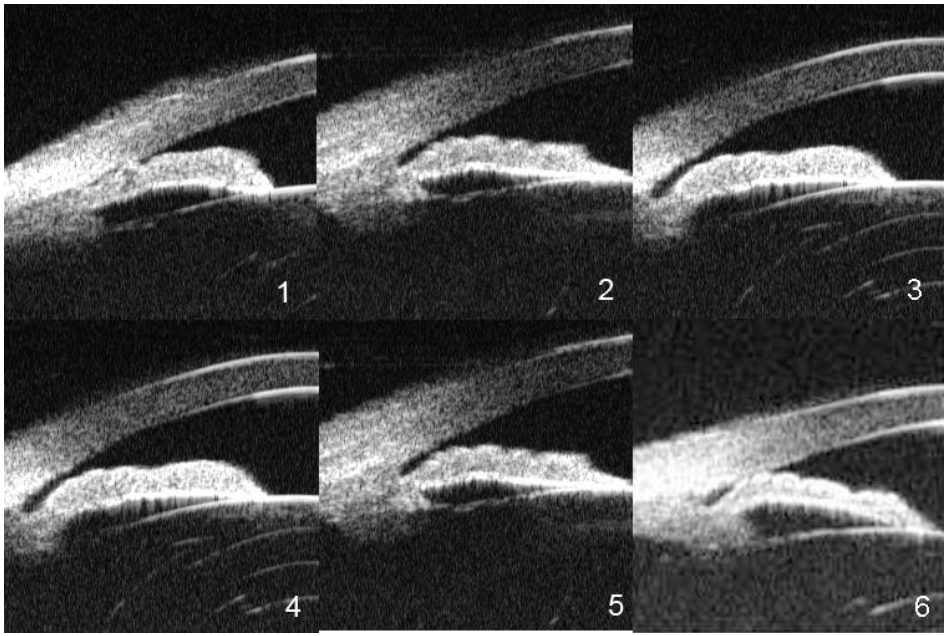


Figure 11 Locations of iris insertion: 1. basal; 2. medium; 3. apical; Angulation iris profile around the location of iris insertion: 4. no angulation; 5. mild angulation; 6 pronounced angulation.

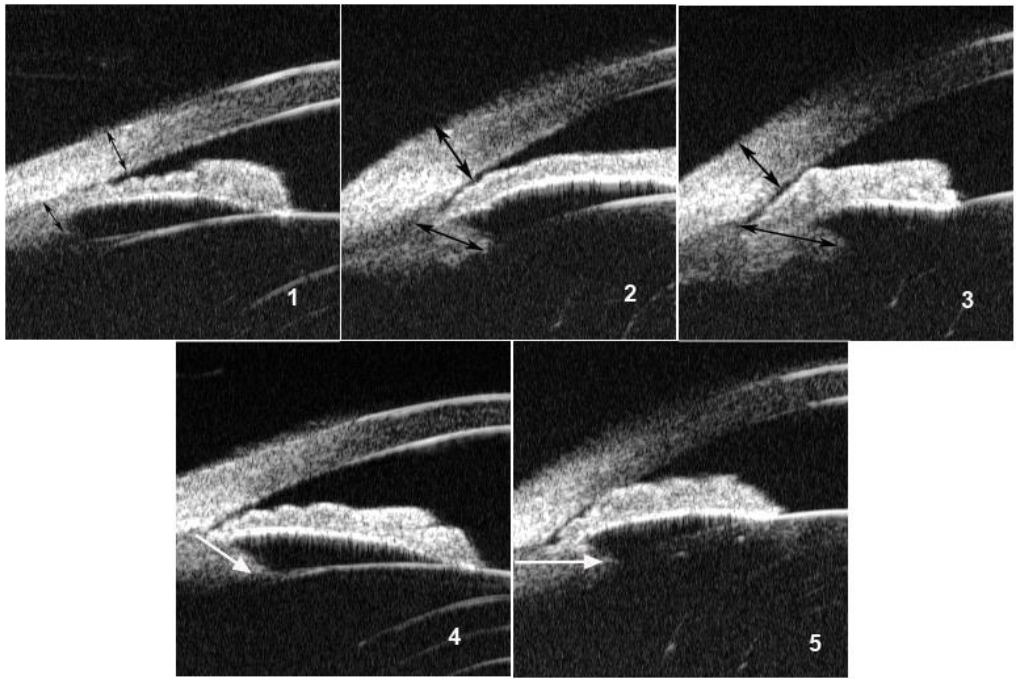


Figure 12 The size of ciliary body was classified according to the relative dimension of the ciliary body in UBM images compared to limbal corneal thickness: 1. small; 2. medium; 3. large. The anatomical position of ciliary body was graded as: 4. neutral; 5. anterior.

7. Changes in Anatomical Features of the Anterior Chamber Angle in Primary Angle-closure Suspects after Laser Peripheral Iridotomy

7.1. Introduction

PACG is estimated to be responsible for approximately half of binocular glaucoma blindness worldwide.[1] Despite the enormous attention that acute angle-closure has drawn, primary angle-closure predominantly presents as a chronic, asymptomatic condition [7-9] . A previous population-based study reported that over 10% of elderly Chinese are asymptomatic suspects at risk of angle-closure. [23] A considerable proportion of angle-closure suspects are at risk of progression to PAC or PACG. [226,242] Laser peripheral iridotomy, a recognised first-line intervention for PACG, helps to prevent acute attacks of angle-closure in the fellow eyes of patients who have suffered from unilateral acute angle-closure [155,185,243]. However, there is no conclusive evidence demonstrating that persons with asymptomatic narrow angles benefit from prophylactic LPI. Previous studies have shown that LPI opens the drainage angle in a majority of PACS cases, whereas angles in a significant minority of eyes remained closed after LPI.[155,230] In the context of limited healthcare resources and budgets, the efficacy of prophylactic LPI needs to be conclusively demonstrated. Furthermore, the harms (if any)

of prophylactic treatment need to be determined.

The study design of the ZAP trial (i.e. treating one randomly selected eye in each participant with LPI and using the fellow untreated eye as the control) provides a unique opportunity to compare the long-term change of angle configuration in eyes with and without intervention by laser treatment. This will also help evaluate the influence of LPI on the natural history of PACS.

7.2. Methods

The width of the anterior chamber angle was assessed using both evaluation under static gonioscopy and quantitative measurements from images acquired by AS-OCT. Detailed methods for gonioscopy and AS-OCT scanning are described in 3.1.3.1.

Statistical analysis

Baseline measures were compared between the treated and untreated eyes using Wilcoxon signed rank tests. Angle width related measures at different visits before and after LPI were compared using one-way repeated measures ANOVA, with inter-visit difference analysed using Tukey's method. All statistical analysis was performed using Stata/SE 13.1 (StataCorp, College Station, TX, USA).

7.3. Results

7.3.1. Immediate Changes in Anatomical Features of Anterior Chamber Angle after LPI

Table 18 compares angle configurations before and 2 weeks after LPI. At 2 weeks after LPI, measures from both gonioscopic assessment and AS-OCT showed the anterior chamber angle width in treated eyes increased markedly compared to baseline. In the untreated eyes, there was no significant change in gonioscopic angle width observed on gonioscopy at 2 weeks after LPI. This finding was in accordance with other gonioscopic findings, namely the number of quadrants with PTM not visible and the range of appositional iridotrabecular contact. All AS-OCT quantitative measures revealed a uniformly significant increase in angle width in treated and untreated eyes (as mentioned in previous chapters, untreated and treated eyes had comparable baseline features, see **Table 20** and **Table 21** for more details) at 2 weeks after LPI, although the magnitude of increase was comparatively much more remarkable in treated eyes.

As shown in **Table 19**, compared to baseline measurements, the magnitudes of changes in angle width measured in AS-OCT images were relatively smaller in women compared to those in men, although the difference was only statistically significant for AOD250 and TISA500.

7.3.2. Longitudinal Analysis of Changes in Anatomical Features of Anterior Chamber Angle after LPI

Data from the following numbers of participants in the ZAP trial were included in this longitudinal analysis of changes in angle width after LPI: 889 at the baseline visit, 884 at 2 weeks after LPI, 864 at 6 months after LPI, 849 at 18 months after LPI and 795 at 36 months after LPI. For further prediction of the trend for longitudinal changes in anterior chamber angle configurations, an incomplete set of data (of 426 participants) from 54 months post-LPI visits was also included in the analysis.

When comparing eyes treated by LPI with untreated eyes, no significant difference was found in baseline features before LPI, including angle width assessed under static gonioscopy, AS-OCT measures (i.e. AOD250, AOD500, AOD750, TISA500, TISA750, and ARA), limbal ACD, iris profile, ocular biometric measures and IOP (**Table 20** and **Table 21**)

7.3.2.1. Trends for Longitudinal Changes in Anterior Chamber Angle Width following LPI

Table 22 to **Table 25** summarise the anterior chamber angle width assessed by both gonioscopy and quantitative analysis of ASOCT images across different visits in treated eyes of men and women. As also shown in **Table 22** to **Table 25** compared to

baseline levels, at 2 weeks after LPI, the anterior chamber angle widened remarkably in treated eyes, gradually decreased over time following laser treatment up to post-LPI 18th months, experienced a slight increase at 36th months after LPI, and then decreased once again with time toward post-LPI 54th months. Although the trend described above seemed to be shared by treated eyes of both men and women, and one-way ANOVA for repeated measures showed statistical significance across different visits in both men and women (P<0.001), multiple comparisons of inter-visit differences using Dunn's test have revealed more significant trend in women.

In the untreated eyes, ever since 2 weeks following LPI, a similar pattern of longitudinal change in angle configuration was observed (**Table 26** to **Table 29**). Similarly, a more significant trend which was consistent across various AS-OCT quantitative measures was observed in untreated eyes of women. In untreated eyes of both men and women, angle width (assessed by both gonioscopic findings and quantitative AS-OCT measurements) was not significantly different at the 18-month and 54-month visit following LPI.

7.3.2.2. Associations of Angle Configuration in Treated and Untreated PACS eyes following LPI

To take into account the individual variability, a mixed effect model was adopted to model the trend of the anterior chamber variables over time. This multi-level model

was set to have the treatment level and the eye level underneath. The model describes each eye with a polynomial curve. The order of the curve was selected to give the lowest Bayesian information criteria (BIC). The mean values and 95% confidence intervals (CI) of the mixed effect models for different AS-OCT quantitative measures of angle configuration were shown in **Figure 19** and **Figure 20**. The 95% CI takes into account both the mixed effect and random effect so that it can reflect the variability of individual eyes. Take AOD500 as an example, the mean trend for treated eyes (depicted as a solid red curve) shows that the angle increases following the LPI. However, the lower bound of 95% CI is below 0 after the LPI, showing decreased angle width over time.

Table 30 shows longitudinal analysis of factors significantly associated with angle configurations of untreated eyes using linear mixed effect models. In accordance with results of one-way ANOVA for repeated measures and Krukal Wallis tests with correction for multiple comparisons, both univariate and multivariate mixed effect models revealed trends for significant decrease in angle width (measured by AS-OCT) with time. Shallower ACD and limbal ACD, as well as plateau iris profile were significantly associated with smaller angle-related AS-OCT measurements (especially AOD250 and TISA500) longitudinally.

Table 31 summarises the proportions of eyes that remained to have narrow angles (identified using two definitions: Definition 1, PTM not visible in at least 180° of

circumference; Definition 2, PTM not visible in at least 270° of circumference) following LPI, as well as the range of iridotrabecular contact at different follow-up visits. In accordance with the trend of longitudinal change in angle width shown above, in treated eyes, the number of eyes with persistent narrow angle (defined by both Definition 1 and Definition 2) decreased markedly from baseline to 2 weeks after LPI, gradually increased from 2 weeks to 18 months following LPI, decreased once again from 18 months to 36 months after LPI, and then slightly increased at 54 months after LPI. Similarly, in treated eyes, the mean number of clock hours with irido-trabecular contact decreased dramatically from 3.14 at baseline to 0.59 at 2 weeks following LPI, increased to 0.68 at 18 months after LPI, and then decreased to 0.42 at 36 months after LPI. All inter-visit differences were statistically significant (P<0.001).

Table 32 compares proportions of both treated and untreated eyes with narrow angles at each follow-up visit. Although men and women followed similar patterns of changes over time, the proportions of eyes with narrow angles defined by Definition 1 (i.e. eyes with PTM not visible under gonioscopy in at least 2 quadrants) were comparatively greater in treated eyes of women at most of the follow-up visits after LPI (no statistical significant differences were found using Chi square tests).

Table 33 shows iris curvature in treated and untreated eyes of men and women at all follow-up visits before LPI and 2 weeks to 36 months after LPI. In both treated and untreated eyes, men and women had similar iris curvature at all visits. Not

unexpectedly, iris curvature decreased remarkably compared to the baseline level immediately following LPI in treated eyes of both men and women. No consistent trend for change in iris curvature in men was found to be in accordance with changes in angle width over time. Most of the multiple comparisons of inter-visit differences in the iris curvature in treated eyes of women, however, were statistically significant in treated eyes of women (**Table 34**).

Lens vault (defined as the perpendicular distance between the anterior pole of the crystalline lens and the line connecting the left and right scleral spurs on an AS-OCT scan [162]), however, seems to be able to offer part of the explanation for the fluctuation in angle width at 36 months post-LPI. As shown in **Table 35**, lens vault gradually increased over time from baseline to 18 months post-LPI in both treated and untreated eyes of men and women, then decreased significantly from 18 months post-LPI to 36 months post-LPI, and finally increased back again at the 54-month follow up after laser treatment.

7.4. Discussion

In this study of longitudinal changes of angle configuration in angle-closure suspects, we observed an overall trend of significant narrowing of the anterior chamber angle over time in both treated and untreated eyes after LPI from 2 weeks to 18 months following the laser treatment. The magnitude of decrease in angle width over time was

significantly more pronounced in eyes without any intervention. After 18 months post-LPI, anterior chamber angles in eyes both treated and untreated by LPI experienced a slight but statistically significant widening and then narrow down again toward 54 months post-LPI.

The finding of remarkably widened drainage angle immediately after LPI is not surprising. Despite of various studies suggesting the possible existence of non-pupil block mechanisms of angle-closure,[153,155,156,232] pupil block is still recognised as a major factor in the development of primary angle-closure. In our study, iris curvature measured in AS-OCT images significantly decreased after LPI (P<0.001). This supports findings of a previous study reporting immediate change in angle width of 176 PACS eyes after LPI,[244] in which AS-OCT scans showed significant widening of the drainage angle along with reduced iris curvature at 1 week after LPI. In contrast to the findings of a previous study that showed a minor and non-significant increase in iris curvature at 18 months compared with immediately after LPI (0.15±0.05 mm vs. 0.16±0.06, P = 0.334),[245] our analysis revealed a slight but significant increase in iris curvature from 2 weeks to 6 months post-LPI (P <0.001) and later a decrease in iris curvature from 6 months to 18 months after LPI.

The current study offers data from a relatively large LPI-treated PACS cohort, and provides further evidence to the theory that non-pupil block mechanisms also play a considerable role in causing primary angle-closure, especially in east Asians. By using

the definition of posterior/pigmented trabecular meshwork not visible under static gonioscopy in at least 2 quadrants, approximately 25% of all eyes had persistent angle-closure after LPI. Over the period of 2 weeks to 18 months post-LPI, this proportion increased in both treated and untreated eyes over time (**Table 31**). If a more stringent definition of angle-closure (i.e., eyes in which posterior/pigmented trabecular meshwork was not visible under static gonioscopy in at least 3 quadrants) was used, the proportions of eyes with persistent angle-closure at follow-up visits in the current study were all relatively lower than the proportion reported from a previous study carried out in the same geographical area.[230,232]

The slow decline in angle width up to the 18th months following LPI in PACS eyes of the current cohort is in accordance with findings of a previous report on PACS over a similar follow-up duration, albeit in a smaller sample.[245] By observing AS-OCT scans in 32 PACS eyes, Lee and et al[245] also found an immediate increase in AOD750 and ARA after LPI and a slow reduction over time up to 18 months after treatment. They suggested that decreased angle width could be due to increased lens vault. In the current study, by the 18th months following LPI, all angle width parameters had demonstrated a decrease relative to the 2-week time-point. In agreement with findings from previous studies, we also found an overall trend of increase in lens vault over time in both eyes treated by LPI and the fellow untreated eyes (**Table 35**).Lens vault measurements in treated eyes were general larger than those in untreated eyes, suggesting the possible existence of an additional effect from LPI on the bulk of the

crystalline lens, especially the contour of its anterior surface.

As the follow-up examinations in the ZAP trial was still on-going at the time of data collection and analysis for this PhD project, data from post-LPI 54th month were only available in 426 eyes. Although a trend for narrowing of the anterior chamber angle from the 36th month to the 54th month after LPI was already revealed with the data available for analysis, futher observation in a longer follow-up period is needed for more conclusive and informative longitudinal change in angle configuration either after prophylactic intervention or as part of the natural history of PACS.

Table 18 Angle Width before and 2 Weeks after Laser Peripheral Iridotomy in Treated and Untreated Eyes

	Treated Eyes [Median (Interquartile Range)]			**Untreated eyes** [Median (Interquartile Range)]		
	Baseline	**Post-LPI 2 weeks**	***P* value**	**Baseline**	**Post-LPI 2 weeks**	***P* value**
Angle Width[§] (°)	13.3 (12.9, 13.7)	25.5 (25.0, 26.0)	<0.001	13.4 (13.0, 13.7)	13.4 (13.0, 13.8)	0.813
Number of Quadrant with PTM not visible [N(%)][†]						
0	0	415		0	9	
1	0	250		0	6	
2	75	120	<0.001	87	80	0.533
3	244	45		237	205	
4	570	59		565	589	
ITC[†] (clock hours)	3.1 (2.9, 3.4)	0.6 (0.5, 0.7)	<0.001	3.2 (3.0, 3.4)	3.4 (3.2, 3.7)	0.129
AOD250[‡] (μm)	38.0 (74.0)	75.5 (86.8)	<0.001	37.0 (72.5)	38.5 (73.5)	<0.001
AOD500[‡] (μm)	71.8 (82.0)	129.3 (97.5)	<0.001	69.0 (74.0)	65.5 (78.0)	<0.001
AOD750[‡] (μm)	116.8 (101.8)	202.5 (112.8)	<0.001	114.5 (84.0)	116.8 (90.5)	<0.001
TISA500[‡] (per 1000 μm^2)	33.5 (31.3)	52.3 (42.3)	<0.001	31.5 (31.5)	34.0 (32.5)	<0.001
TISA750[‡] (per 1000 μm^2)	69.0 (58.3)	107.0 (65.3)	<0.001	65.5 (55.5)	68.3 (56.0)	<0.001
ARA[‡] (per 1000 μm^2)	72.5 (67.8)	111.5 (79.5)	<0.001	68.5 (60.5)	72.5 (67.5)	<0.001

† Number of eyes, PTM: posterior/pigmented trabecular meshwork; ITC: iridotrabecular contact; ‡ PACS: primary angle-closure suspect,; AOD: angle opening distance; TISA: trabecular-iris space area; ARA: angle recess area; [§] Values shown are means (standard deviations)

Table 19 Comparison of Immediate Change in Angle Width after LPI† between Treated Eyes of Men and Women

Immediate Change after LPI	**Men** [Median (Interquartile Range)]	**Women** [Median (Interquartile Range)]	***P* values‡**
Angle Width (°)	12.5 (10.0)	12.5 (10.0)	0.59
AOD250 (μm)†	51.8 (88.5)	36.8 (74.5)	0.044
AOD500 (μm)†	62.3 (88.5)	52.0 (79.5)	0.15
AOD750 (μm)†	104.3 (90.8)	85.3 (92.0)	0.19
TISA500 (1000 μm^2)†	29.5 (36.3)	20.3 (33.0)	0.011
TISA750 (1000 μm^2)†	53.2 (61.0)	39.8 (55.5)	0.047
ARA (1000 μm^2)†	54.0 (67.0)	43.8 (67.0)	0.07

† LPI: laser peripheral iridotomy, AOD: angle opening distance; TISA: trabecular-iris space area; ARA: angle recess area; PTM: posterior/pigmented trabecular meshwork

‡ Wilcoxon signed rank test was used

Table 20 Comparison of Baseline Measures between Treated and Untreated Eyes of Men [Median (Interquartile Range)]

	Treated Eyes	**Untreated eyes**	***P* value**
Angle width on gonioscopy (°)‡	14.7 (5.8)	14.9 (6.1)	0.75
Intraocular Pressure (mmHg)‡	15.0 (3.1)	14.8 (3.1)	0.49
van Herick Score [N(%)]§			
5%	3 (2.0)	4 (2.6)	
15%	31 (20.4)	27 (17.8)	
25%	104 (68.4)	109 (71.7)	0.72
40%	12 (7.9)	10 (6.7)	
75%	2 (1.3)	2 (1.3)	
Iris profile [N(%)]§			
Steep	108 (72.5)	110 (72.9)	
Regular	30 (20.1)	30 (19.9)	0.005
Plateau	11 (7.4)	11 (7.3)	
Axial Length (mm)	22.8 (1.0)	22.8 (0.9)	0.61
ACD (mm)†	2.5 (0.3)	2.6 (0.3)	0.06
Lens thickness (mm)	5.0 (0.4)	4.9 (0.4)	0.50
ITC (clock hours)†	2.5 (4)	1 (3)	0.53
AOD250 (μm)†	40.0 (71.5)	22.0 (78.0)	0.24
AOD500 (μm)†	83.0 (81.5)	69.0 (71.5)	0.22
AOD750 (μm)†	138.0 (108.5)	130.0 (95.0)	0.29
TISA500 (1000 μm^2)†	35.5 (30.5)	29.5 (39.0)	0.29
TISA750 (1000 μm^2)†	74.0 (54.5)	61.5 (59.0)	0.24
ARA (1000 μm^2)†	75.0 (72.5)	66.5 (62.0)	0.20

† ACD: anterior chamber angle; AOD: angle opening distance; TISA: trabecular-iris space area; ARA: angle recess area; ITC: iridotrabecular contact

§ Chi-square test; ‡ values shown are means (standard deviations)

Table 21 Comparison of Baseline Measures between Treated and Untreated Eyes of Women [Median (Interquartile Range)]

	Treated Eyes	Untreated eyes	*P* value
Angle width on gonioscopy (°)‡	13.1 (5.9)	13.0 (5.9)	0.94
Intraocular Pressure (mmHg)	15.1 (2.8)	15.2 (2.8)	0.63
van Herick Score [N(%)]§			
5%	29 (3.93)	27 (3.7)	
15%	240 (32.6)	235 (31.89)	
25%	439 (59.6)	449 (60.8)	0.44
40%	26 (3.5)	25 (3.4)	
75%	3 (0.4)	2 (0.3)	
Iris profile [N(%)]§			
Steep	548 (74.7)	554 (75.5)	
Regular	130 (17.7)	123 (16.8)	0.23
Plateau	56 (7.6)	57 (7.8)	
Axial Length (mm)	22.5 (0.9)	22.4 (0.9)	0.95
ACD (mm)†	2.6 (0.3)	2.5 (0.3)	0.52
Lens thickness (mm)	4.9 (0.4)	4.9 (0.4)	0.47
ITC (clock hours)†	3 (5)	3 (5)	0.53
AOD250 (μm)†	37.5 (74.5)	37.5 (71.0)	0.80
AOD500 (μm)†	68.5 (80.0)	65.5 (77.0)	0.26
AOD750 (μm)†	113.0 (98.5)	113.3 (86.0)	0.78
TISA500 (1000 μm^2)†	32.5 (32.0)	32.0 (31.5)	0.57
TISA750 (1000 μm^2)†	67.0 (59.0)	66.3 (54.5)	0.81
ARA (1000 μm^2)†	71.0 (67.5)	69.0 (61.0)	0.88

† ACD: anterior chamber angle; AOD: angle opening distance; TISA: trabecular-iris space area; ARA: angle recess area; ITC: iridotrabecular contact

§ Chi-square test; ‡ values shown are means (standard deviations)

Table 22 Change of Angle Configuration over Time in Treated Eyes of Men [Median (Interquartile Range)]

	Angle Width(°) ‡	AOD† 250(μm)	AOD† 500(μm)	AOD† 750(μm)	TISA† 500 (per 1000 μm²)	TISA† 750 (per 1000 μm²)	ARA† (per 1000 μm²)
Baseline	14.7 (5.8)	40.0 (71.5)	83.0 (81.5)	138.0 (108.5)	35.5 (30.5)	74.0 (54.5)	75.0 (72.5)
Post-LPI† 2 weeks	26.7 (6.3)	90.5 (107.5)	144.0 (101.5)	226.5 (117.0)	60.5 (45.5)	118.0 (76.5)	124. (91.5)
Post-LPI† 6 months	25.9 (6.8)	78.3 (88.5)	128.5 (94.5)	209.8 (101.3)	54.5 (46.5)	109.5 (72.5)	115.0 (98.8)
Post-LPI† 18 months	24.4 (7.5)	58.5 (107.5	99.0 (117.8)	177.0 (112.5)	41.5 (44.8)	88.0 (74.5)	96.5 (90.5)
Post-LPI† 36 months	29.4 (8.0)	90.9 (78.1)	145.1 (105.8)	225.3 (100.3)	60.4 (40.0)	122.3 (63.0)	131.8 (79.0)
Post-LPI† 54 months§	24.8 (9.0)	70.4 (74.7)	110.3 (77.7)	189.2 (67.4)	47.7 (31.7)	96.8 (50.6)	101.9 (58.6)

† AOD: angle opening distance; TISA: trabecular-iris space area; ARA: angle recess area; LPI: laser peripheral iridotomy. § Number of participants with data available from 54-month follow-up visit: 58. ‡ Values shown for gonioscopic angle width are means(standard deviation)

Table 23 Statistical Significance of Inter-visit Comparison of Angle Configurations after Laser Peripheral Iridotomy (Men) §

	Angle Width	AOD† 250	AOD† 500	AOD† 750	TISA† 500	TISA† 750	ARA†
Post-LPI† 2 weeks vs 6 months	1.00	1.00	0.33	0.61	1.00	0.89	1.00
Post-LPI† 2 weeks vs 18 months	0.029	0.005	<0.001	<0.001	<0.001	<0.001	<0.001
Post-LPI† 2 weeks vs 36 months	0.009	1.00	1.00	1.00	1.00	1.00	1.00
Post-LPI† 6 months vs 18 month	0.26	0.053	0.07	0.029	0.018	0.008	0.016
Post-LPI† 6 month vs 36 month	<0.001	1.00	0.21	0.64	1.00	0.27	0.56
Post-LPI† 18 month vs 36 month	<0.001	0.009	<0.001	<0.001	<0.001	<0.001	<0.001
Post-LPI† 36 month vs 54 month	<0.001	0.056	0.035	0.13	0.042	0.005	0.007
Post-LPI† 18 month vs 54 month	1.00	1.00	1.00	1.00	1.00	1.00	1.00

† AOD: angle opening distance; TISA: trabecular-iris space area; ARA: angle recess area; LPI: laser peripheral iridotomy; § Dunn's tests were used for correction for multiple comparison based on Kruskal Wallis test

Table 24 Change of Angle Configuration over Time in Treated Eyes of Women [Median (Interquartile Range)]

	Angle Width(°)	AOD† 250(μm)	AOD† 500(μm)	AOD† 750(μm)	TISA† 500 (per 1000 μm^2)	TISA† 750 (per 1000 μm^2)	ARA† (per 1000 μm^2)
Post-LPI† 2 weeks	25.3 (7.1)	75.5 (86.8)	125.5 (93.5)	198.0 (109.5)	52.0 (42.0)	104.5 (63.5)	109.5 (75.0)
Post-LPI† 6 months	25.7 (7.1)	73.0 (89.0)	118.0 (84.0)	177.5 (97.0)	50.5 (44.5)	100.0 (68.5)	107.0 (93.0)
Post-LPI† 18 months	23.9 (7.2)	56.0 (83.0)	99.0 (92.0)	163.0 (96.0)	42.5 (40.5)	88.0 (66.0)	91.0 (77.5)
Post-LPI† 36 months	28.4 (8.6)	77.0 (77.7)	138.2 (81.5)	206.9 (99.8)	54.6 (37.9)	110.3 (56.1)	118.5 (69.2)
Post-LPI† 54 months§	25.0 (9.1)	73.4 (75.1)	120.1 (83.0)	193.9 (104.0)	51.9 (38.2)	101.2 (56.1)	112.7 (69.4)

† AOD: angle opening distance; TISA: trabecular-iris space area; ARA: angle recess area; LPI: laser peripheral iridotomy. § Number of participants with data available from 54-month follow-up visit: 252. ‡ Values shown for gonioscopic angle width are means(standard deviation)

Table 25 Statistical Significance of Inter-visit Comparison of Angle Configurations after Laser Peripheral Iridotomy (Women) §

	Angle Width	AOD† 250	AOD† 500	AOD† 750	TISA† 500	TISA† 750	ARA†
Post-LPI† 2 weeks vs 6 months	1.00	1.00	0.06	<0.001	1.00	1.00	1.00
Post-LPI† 2 weeks vs 18 months	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Post-LPI† 2 weeks vs 36 months	<0.001	1.00	0.008	0.09	1.00	0.75	0.69
Post-LPI† 6 months vs 18 month	<0.001	<0.001	<0.001	0.005	<0.001	<0.001	<0.001
Post-LPI† 6 month vs 36 month	<0.001	0.84	<0.001	<0.001	0.91	0.042	0.15
Post-LPI† 18 month vs 36 month	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Post-LPI† 36 month vs 54 month	<0.001	0.97	0.08	0.11	1.00	0.19	0.60
Post-LPI† 18 month vs 54 month	0.012	0.013	<0.001	<0.001	0.001	0.001	<0.001

† AOD: angle opening distance; TISA: trabecular-iris space area; ARA: angle recess area; LPI: laser peripheral iridotomy; § Dunn's tests were used for correction for multiple comparison based on Kruskal Wallis test

Table 26 Change of Angle Configuration over Time in Untreated Eyes of Men [Median (Interquartile Range)]

	Angle Width(°) ‡	AOD† 250(μm)	AOD† 500(μm)	AOD† 750(μm)	TISA† 500 (per 1000 μm^2)	TISA† 750 (per 1000 μm^2)	ARA† (per 1000 μm^2)
Post-LPI† 2 weeks	14.8 (5.4)	37.5 (68.3)	73.3 (87.8)	116.8 (123.7)	33.3 (37.8)	70.3 (67.8)	74.3 (71.0)
Post-LPI† 6 months	13.5 (5.7)	20.5 (63.0)	51.5 (83.0)	111.5 (96.5)	26.5 (30.5)	57.5 (47.0)	59.0 (55.0)
Post-LPI† 18 months	12.2 (5.5)	17.5 (54.0)	39.5 (85.5)	112.0 (108.2)	19.8 (30.0)	49.1 (53.0)	49.5 (58.5)
Post-LPI† 36 months	13.1 (7.8)	21.1 (61.9)	74.2 (74.0)	136.1 (113.1)	27.0 (26.2)	62.3 (56.4)	64.6 (61.5)
Post-LPI† 54 months§	11.0 (8.3)	19.8 (41.4)	40.7 (61.4)	98.6 (66.1)	19.5 (24.8)	48.1 (39.3)	48.1 (41.1)

† AOD: angle opening distance; TISA: trabecular-iris space area; ARA: angle recess area; LPI: laser peripheral iridotomy. § Number of participants with data available from 54-month follow-up visit: 247. ‡ Values shown for gonioscopic angle width are means(standard deviation)

Table 27 Statistical Significance of Inter-visit Comparison of Angle Configurations after Laser Peripheral Iridotomy (Men, Untreated Eyes) §

	Angle Width	AOD† 250	AOD† 500	AOD† 750	TISA† 500	TISA† 750	ARA†
Post-LPI† 2 weeks vs 6 months	0.82	0.68	0.06	0.24	0.18	0.24	0.38
Post-LPI† 2 weeks vs 18 months	<0.001	0.029	<0.001	0.044	<0.001	<0.001	<0.001
Post-LPI† 2 weeks vs 36 months	1.00	1.00	1.00	1.00	0.09	1.00	1.00
Post-LPI† 6 months vs 18 month	0.001	0.95	0.48	1.00	0.08	0.11	0.11
Post-LPI† 6 month vs 36 month	0.11	1.00	0.19	0.29	1.00	1.00	1.00
Post-LPI† 18 month vs 36 month	<0.001	0.75	0.002	0.06	0.36	0.037	0.044
Post-LPI† 36 month vs 54 month	<0.001	1.00	0.021	0.21	0.70	0.12	0.17
Post-LPI† 18 month vs 54 month	0.85	1.00	1.00	1.00	1.00	1.00	1.00

† AOD: angle opening distance; TISA: trabecular-iris space area; ARA: angle recess area; LPI: laser peripheral iridotomy; § Dunn's tests were used for correction for multiple comparison based on Kruskal Wallis test

Table 28 Change of Angle Configuration over Time in Untreated Eyes of Women [Median (Interquartile Range)]

	Angle Width(°) ‡	AOD† 250(μm)	AOD† 500(μm)	AOD† 750(μm)	TISA† 500 (per 1000 μm^2)	TISA† 750 (per 1000 μm^2)	ARA† (per 1000 μm^2)
Post-LPI† 2 weeks	13.1 (6.2)	38.7 (74.0)	64.5 (73.5)	116.8 (85.5)	34.0 (31.5)	68.0 (54.5)	72.5 (67.0)
Post-LPI† 6 months	12.0 (6.1)	34.0 (61.5)	56.0 (74.0)	97.0 (88.5)	28.5 (31.5)	59.0 (51.5)	60.5 (63.0)
Post-LPI† 18 months	11.2 (5.6)	19.1 (54.5)	40.0 (79.5)	84.5 (98.5)	20.5 (30.5)	46.6 (55.0)	49.0 (59.0)
Post-LPI† 36 months	11.8 (7.7)	20.5 (60.2)	59.5 (80.2)	119.7 (108.1)	23.1 (30.0)	59.7 (53.7)	60.3 (61.9)
Post-LPI† 54 months§	9.5 (6.6)	20.1 (59.3)	43.9 (91.5)	104.1 (98.1)	25.9 (35.0)	50.6 (60.4)	53.5 (67.4)

† AOD: angle opening distance; TISA: trabecular-iris space area; ARA: angle recess area; LPI: laser peripheral iridotomy. § Number of participants with data available from 54-month follow-up visit: 247. ‡ Values shown for gonioscopic angle width are means(standard deviation)

Table 29 Statistical Significance of Inter-visit Comparison of Angle Configurations after Laser Peripheral Iridotomy (Women, Untreated Eyes) §

	Angle Width	AOD† 250	AOD† 500	AOD† 750	TISA† 500	TISA† 750	ARA†
Post-LPI† 2 weeks vs 6 months	0.82	0.004	<0.001	<0.001	<0.001	<0.001	0.005
Post-LPI† 2 weeks vs 18 months	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Post-LPI† 2 weeks vs 36 months	1.00	<0.001	0.043	1.00	<0.001	0.003	<0.001
Post-LPI† 6 months vs 18 month	0.001	<0.001	0.001	0.046	<0.001	<0.001	<0.001
Post-LPI† 6 month vs 36 month	0.11	0.46	0.35	<0.001	0.007	1.00	1.00
Post-LPI† 18 month vs 36 month	<0.001	0.08	<0.001	<0.001	0.17	<0.001	<0.001
Post-LPI† 36 month vs 54 month	<0.001	1.00	0.07	0.026	1.00	0.09	0.22
Post-LPI† 18 month vs 54 month	0.85	0.62	0.37	0.017	0.15	1.00	1.00

† AOD: angle opening distance; TISA: trabecular-iris space area; ARA: angle recess area; LPI: laser peripheral iridotomy; § Dunn's tests were used for correction for multiple comparison based on Kruskal Wallis test

Table 30 An Examination of Factors Associated with Longitudinal Changes in Angle Configuration

(Untreated Eyes, Mixed Effect Models)

	Angle Width (°)	AOD250† (μm)	AOD500† (μm)	AOD750† (μm)	TISA500† (1000 μm^2)	TISA750† (1000 μm^2)	ARA† (1000 μm^2)
Univariate Analysis							
Time	0.002	-0.061**	-0.060**	-0.038**	-0.049**	-0.065**	-0.091**
Multivariate Analysis							
Time	0.003	-0.060**	-0.046**	-0.015	-0.047**	-0.064**	-0.091**
ACD†	2.963**	14.001**	54.574**	96.855**	13.355**	9.426	7.825
Baseline Limbal ACD†	0.148**	0.572**	0.831**	1.067**	0.399**	0.399**	0.638**
Iris Profile							
Regular	0.189	2.421	6.609**	12.597**	0.511	4.915	6.189
Plateau	-2.303**	-9.362**	-0.112	12.519**	-5.517**	-6.769	-8.311

§ Data from visits at 54 months following LPI were availab le in only 310 participants. † Values listed are regression coefficient (95% Confidence Intervals); AOD: angle opening distance; TISA: trabecular-iris space area; ARA: angle recess area; ACD: anterior chamber depth; limbal ACD was measured using van Herick scores. ** p<0.01, * p<0.05

Table 31 Proportions of Eyes with Narrow Angles and Range of Iridotrabecular Apposition [Mean (SD)]

	Treated Eyes			Untreated Eyes		
	Angle-closure [n (% of total)]		ITA†	Angle-closure [n (% of total)]		ITA†
	Definition 1§	Definition 2§	(clockhours)	Definition 1§	Definition 2§	(clockhours)
Baseline	889 (100.0)	814 (91.56)	3.14 (3.29)	889 (100.0)	802 (90.2)	3.20 (3.40)
Post-LPI 2 weeks	224 (25.3)	104 (11.76)	0.59 (1.40)	874 (98.9)	794 (89.8)	3.41 (3.67)
Post-LPI 6 months	255 (29.5)	118 (13.66)	0.49 (1.29)	855 (99.0)	786 (91.0)	3.50 (3.50)
Post-LPI 18 months	362 (42.6)	152 (17.90)	0.68 (1.39)	840 (99.0)	777 (91.5)	3.11 (2.82)
Post-LPI 36 months	234 (29.4)	123 (15.47)	0.42 (1.31)	766 (96.4)	679 (85.4)	3.44 (3.23)
Post-LPI 54 months‡	158 (37.1)	75 (17.61)	0.36 (1.15)	412 (96.7)	381 (89.4)	2.16 (3.17)

† ITA: mean range of iridotrabecular appositional contact; LPI: laser peripheral iridotomy

§ Definition 1 of narrow angle: posterior/pigmented trabecular meshwork not visible in at least 180-degree circumference under static gonioscopy. Definition 2 of narrow angle: posterior/pigmented trabecular meshwork not visible in at least 270-degree circumference under static gonioscopy.

‡ Gonioscopic measures at post-LPI 54 months are available in only 426 eyes

Table 32 Proportions of Eyes with Narrow Angles in Treated Eyes before and after Laser Peripheral Iridotomy in Men and Women [Mean (SD)]

	Definition 1§ [n (% of total)]		Definition 2§ [n (% of total)]	
	Men	**Women**	**Men**	**Women**
Baseline	152 (100.0)	737(100.0)	129 (84.9)	685 (92.9)
Post-LPI 2 weeks	27 (17.9)	197 (26.9)	11 (7.3)	93 (12.7)
Post-LPI 6 months	34 (23.0)	221 (30.9)	17 (11.5)	101 (14.1)
Post-LPI 18 months	62 (41.9)	300 (42.8)	28 (18.9)	124 (17.7)
Post-LPI 36 months	38 (27.1)	196 (29.9)	21 (15.0)	102 (15.6)
Post-LPI 54 months‡	30 (38.5)	128 (36.8)	15 (19.2)	60 (17.2)

§ Definition 1 of narrow angle: posterior/pigmented trabecular meshwork not visible in at least 180-degree circumference under static gonioscopy. Definition 2 of narrow angle: posterior/pigmented trabecular meshwork not visible in at least 270-degree circumference under static gonioscopy.

‡ Measurements at post-LPI 54 months are available in only 426 eyes

Table 33 Change in Iris Curvature (in Dark) before and after Laser Peripheral Iridotomy (mm) [Mean (SD)]

	Treated Eye			Untreated Eyes		
	Men	**Women**	***P* value†**	**Men**	**Women**	***P* value†**
Baseline	0.38 (0.22)	0.41 (0.26)	0.35	0.38 (0.22)	0.42 (0.27)	0.15
Post-LPI 2 weeks	0.26 (0.32)	0.27 (0.29)	0.60	0.38 (0.23)	0.41 (0.26)	0.20
Post-LPI 6 months	0.32 (0.38)	0.34 (0.37)	0.52	0.39 (0.25)	0.43 (0.28)	0.13
Post-LPI 18 months	0.24 (0.30)	0.27 (0.28)	0.32	0.40 (0.24)	0.43 (0.25)	0.23
Post-LPI 36 months	0.29 (0.37)	0.22 (0.24)	0.02	0.40 (0.23)	0.41 (0.26)	0.66
Post-LPI 54 months‡	0.17 (0.20)	0.21 (0.22)	0.20	0.32 (0.10)	0.38 (0.20)	0.02

§ Definition 1 of narrow angle: posterior/pigmented trabecular meshwork not visible in at least 180-degree circumference under static gonioscopy. Definition 2 of narrow angle: posterior/pigmented trabecular meshwork not visible in at least 270-degree circumference under static gonioscopy.

‡ Measurements at 54 months afte LPI are available in only 426 eyes; † P values from Student t tests for comparisons between men and women

Table 34 *P* values for Inter-visit Comparision of Iris Curvature (in Dark) in Treated and Untreated Eyes [Mean (SD)]

	Treated Eyes		Untreated Eyes	
	Men	**Women**	**Men**	**Women**
Baseline vs Post-LPI 2 Weeks	0.036	<0.001	1.00	1.00
Baseline vs Post-LPI 6 Months	0.37	<0.001	1.00	0.52
Baseline vs Post-LPI 18 Months	0.01	<0.001	0.99	0.94
Baseline vs Post-LPI 36 Months	0.17	<0.001	0.99	0.62
Baseline vs Post-LPI 54 Months	<0.001	<0.001	0.27	0.33
Post-LPI 2 Weeks vs Post-LPI 6 Months	0.86	0.002	1.00	0.65
Post-LPI 2 Weeks vs Post-LPI 18 Months	1.00	0.90	0.99	0.98
Post-LPI 2 Weeks vs Post-LPI 36 Months	1.00	<0.001	0.99	0.42
Post-LPI 2 Weeks vs Post-LPI 54 Months	0.34	<0.001	0.21	0.21
Post-LPI 6 Months vs Post-LPI 18 Months	0.62	<0.001	1.00	0.96
Post-LPI 6 Months vs Post-LPI 36 Months	0.98	<0.001	1.00	0.013
Post-LPI 6 Months vs Post-LPI 54 Months	0.04	<0.001	0.11	0.009
Post-LPI 18 Months vs Post-LPI 36 Months	0.98	0.006	1.00	0.11
Post-LPI 18 Months vs Post-LPI 54 Months	0.47	0.008	0.06	0.06
Post-LPI 36 Months vs Post-LPI 54 Months	0.22	0.99	0.08	0.97
Overall Comparison across All Visits†	0.001	<0.001	0.18	0.053

† Overall comparisons across all visits were performed using two-way ANOVA for repeated measures

Table 35 Longitudinal Changes in Lens Vault in Men and Women (μm) [Median (Interquartile Range)]

	Treated Eyes			Untreated Eyes		
	Men	**Women**	***P* value**	**Men**	**Women**	***P* value**
Baseline	712.5 (289.8)	747.0 (286.9)	0.24	746.2 (315.4)	751.8 (290.8)	0.91
Post-LPI 2 weeks	763.9 (327.4)	781.0 (308.9)	0.65	727.6 (305.7)	750.7 (289.5)	0.69
Post-LPI 6 months	769.8 (375.8)	811.9 (331.0)	0.37	756.6 (308.8)	776.6 (294.1)	0.71
Post-LPI 18 months	882.5 (373.6)	875.4 (309.9)	0.88	764.3 (310.1)	806.4 (306.3)	0.82
Post-LPI 36 months	764.8 (371.0)	807.9 (292.9)	0.037	697.0 (282.9)	706.8 (273.0)	0.73
Post-LPI 54 months‡	867.8 (226.9)	868.3 (276.7)	0.83	789.2 (271.6)	778.3 (280.1)	0.66

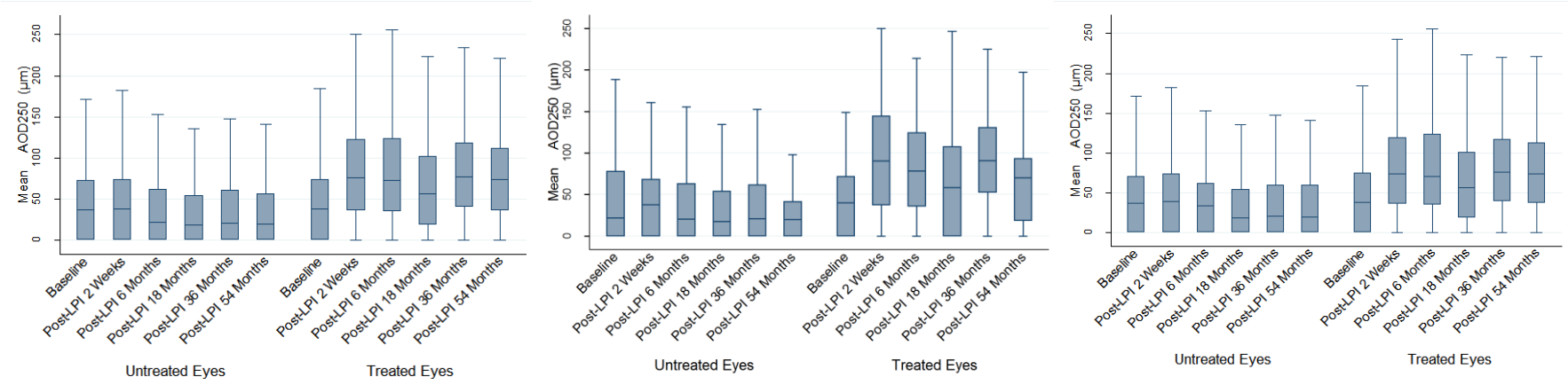
§ Definition 1 of narrow angle: posterior/pigmented trabecular meshwork not visible in at least 180-degree circumference under static gonioscopy. Definition 2 of narrow angle: posterior/pigmented trabecular meshwork not visible in at least 270-degree circumference under static gonioscopy.

‡ Measurements at 54 months afte LPI are available in only 426 eyes; † P values from Student t tests for comparisons between men and women

Table 36 *P* values for Inter-visit Comparision of Lens Vault in Treated and Untreated Eyes [Mean (SD)]

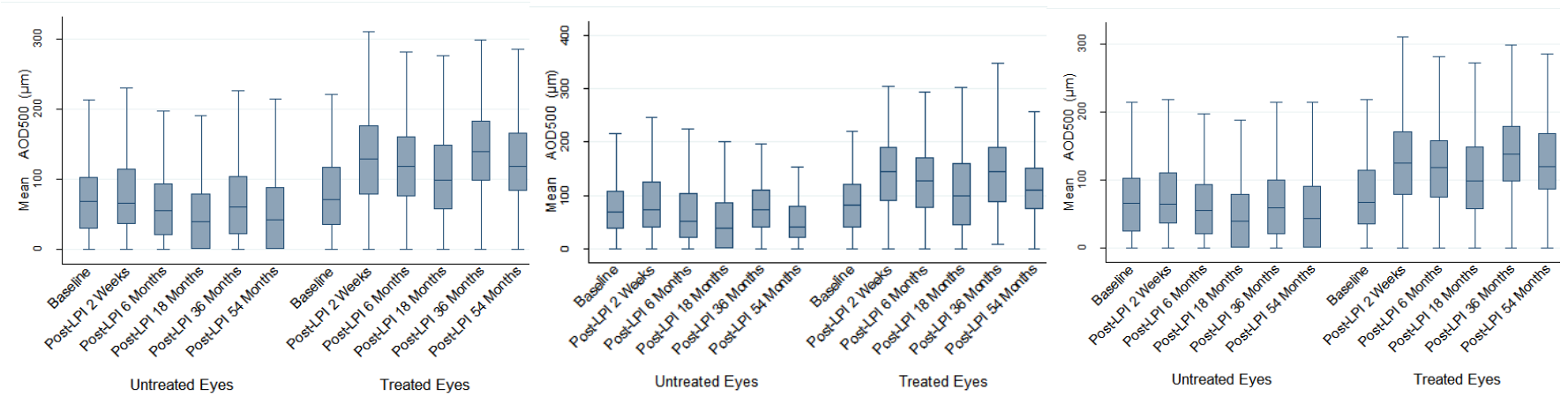
	Treated Eyes		Untreated Eyes	
	Men	**Women**	**Men**	**Women**
Baseline vs Post-LPI 2 Weeks	0.95	0.46	1.00	1.00
Baseline vs Post-LPI 6 Months	0.82	0.39	0.77	0.33
Baseline vs Post-LPI 18 Months	<0.001	<0.001	0.054	<0.001
Baseline vs Post-LPI 36 Months	0.99	0.002	0.40	0.019
Baseline vs Post-LPI 54 Months	0.001	<0.001	0.01	0.001
Post-LPI 2 Weeks vs Post-LPI 6 Months	1.00	1.00	0.41	0.08
Post-LPI 2 Weeks vs Post-LPI 18 Months	0.003	<0.001	0.008	<0.001
Post-LPI 2 Weeks vs Post-LPI 36 Months	1.00	0.22	0.66	0.06
Post-LPI 2 Weeks vs Post-LPI 54 Months	0.007	<0.001	0.002	<0.001
Post-LPI 6 Months vs Post-LPI 18 Months	0.005	<0.001	0.57	0.024
Post-LPI 6 Months vs Post-LPI 36 Months	0.99	0.24	0.012	<0.001
Post-LPI 6 Months vs Post-LPI 54 Months	0.011	<0.001	0.14	0.09
Post-LPI 18 Months vs Post-LPI 36 Months	0.003	<0.001	<0.001	<0.001
Post-LPI 18 Months vs Post-LPI 54 Months	0.98	0.94	0.83	1.00
Post-LPI 36 Months vs Post-LPI 54 Months	0.004	<0.001	<0.001	<0.001
Overall Comparison across All Visits†	<0.001	<0.001	<0.001	<0.001

† Overall comparisons across all visits were performed using two-way ANOVA for repeated measures



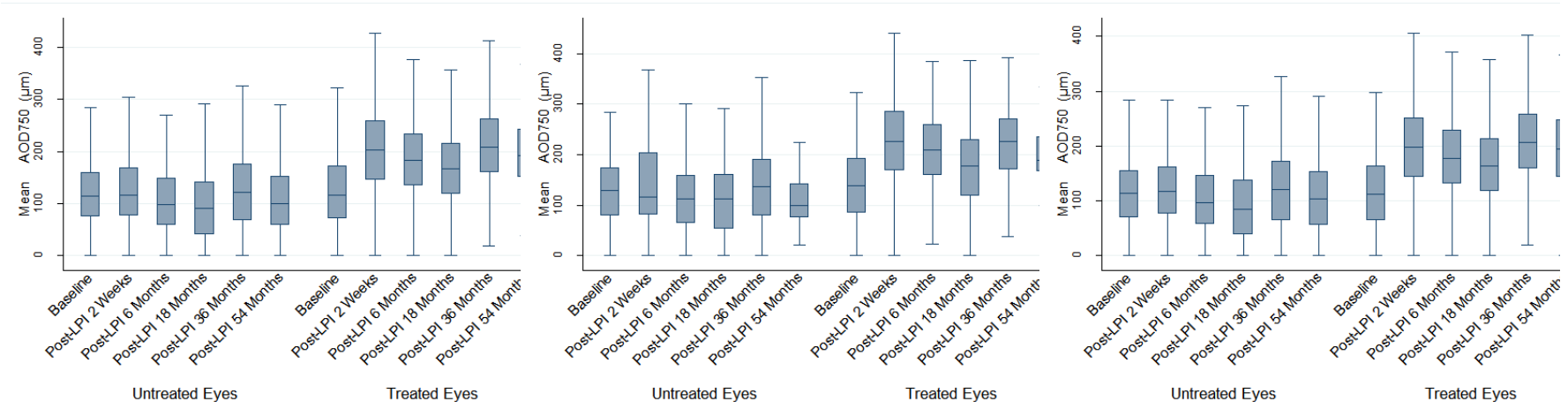
All Study Participants **Men** **Women**

Figure 13 Longitudinal Changes in AOD250 (AOD: angle opening distance, Whiskers in box plots extends to 1.5 times of the interquartile range)



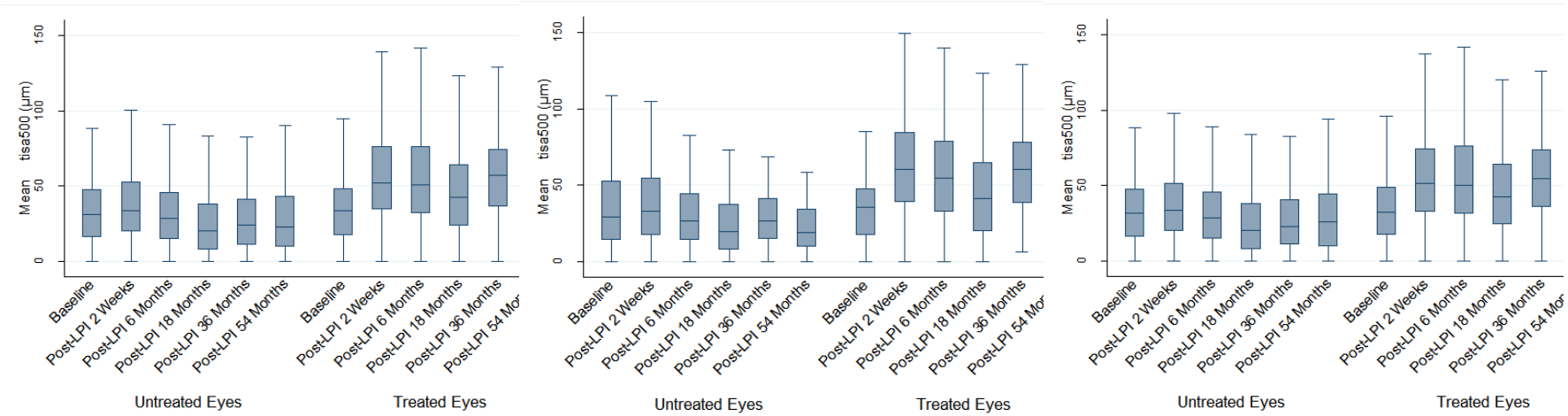
All Study Participants **Men** **Women**

Figure 14 Longitudinal Changes in AOD500 (AOD: angle opening distance, Whiskers in box plots extends to 1.5 times of the interquartile range)



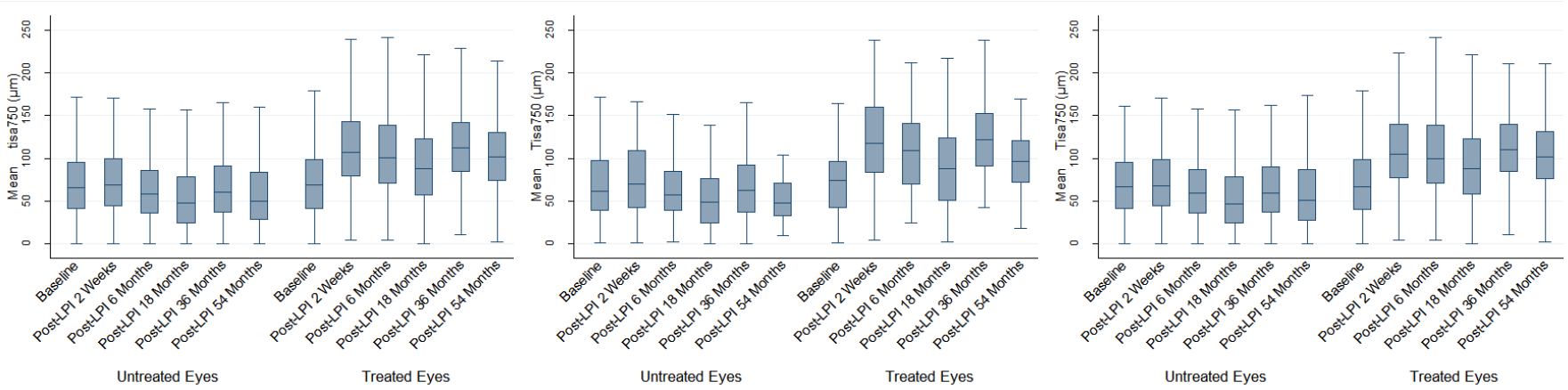
All Study Participants **Men** **Women**

Figure 15 Longitudinal Changes in AOD750 (AOD: angle opening distance, Whiskers in box plots extends to 1.5 times of the interquartile range)



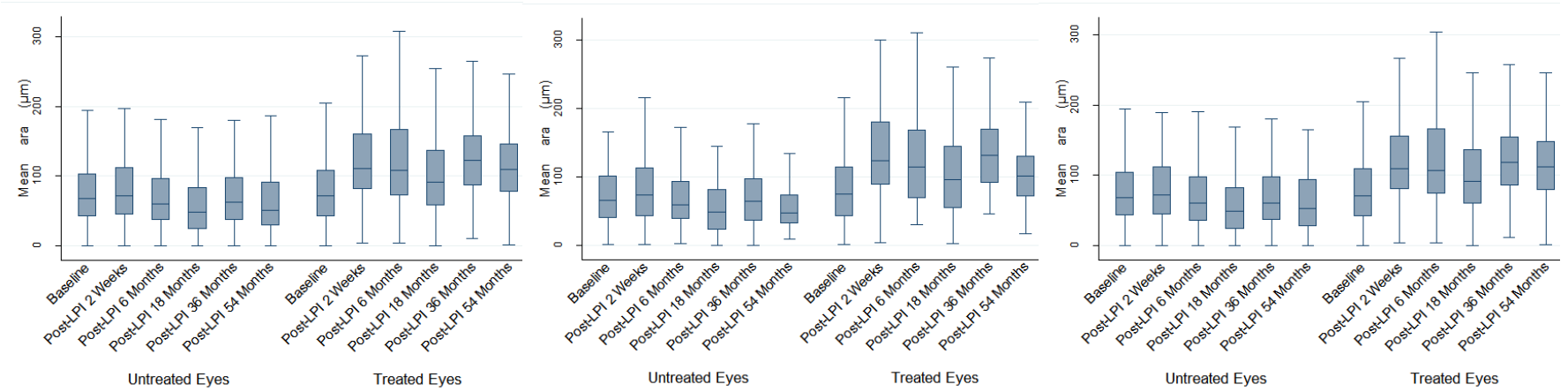
All Study Participants **Men** **Women**

Figure 16 Longitudinal Changes in TISA500 (TISA: trabecular iris space area, Whiskers in box plots extends to 1.5 times of the interquartile range)



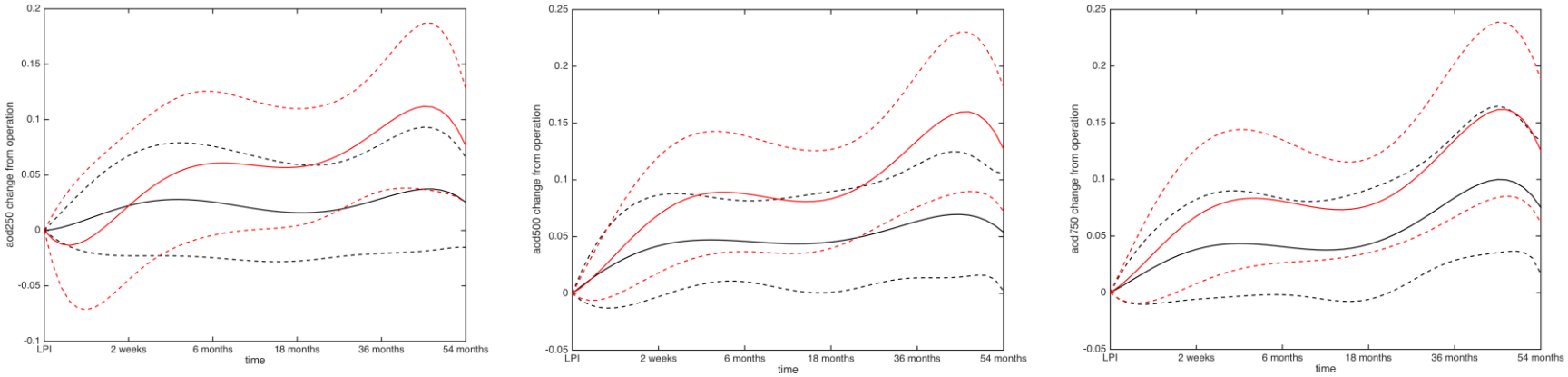
All Study Participants **Men** **Women**

Figure 17 Longitudinal Changes in TISA750 (TISA: trabecular iris space area, Whiskers in box plots extends to 1.5 times of the interquartile range)



All Study Participants **Men** **Women**

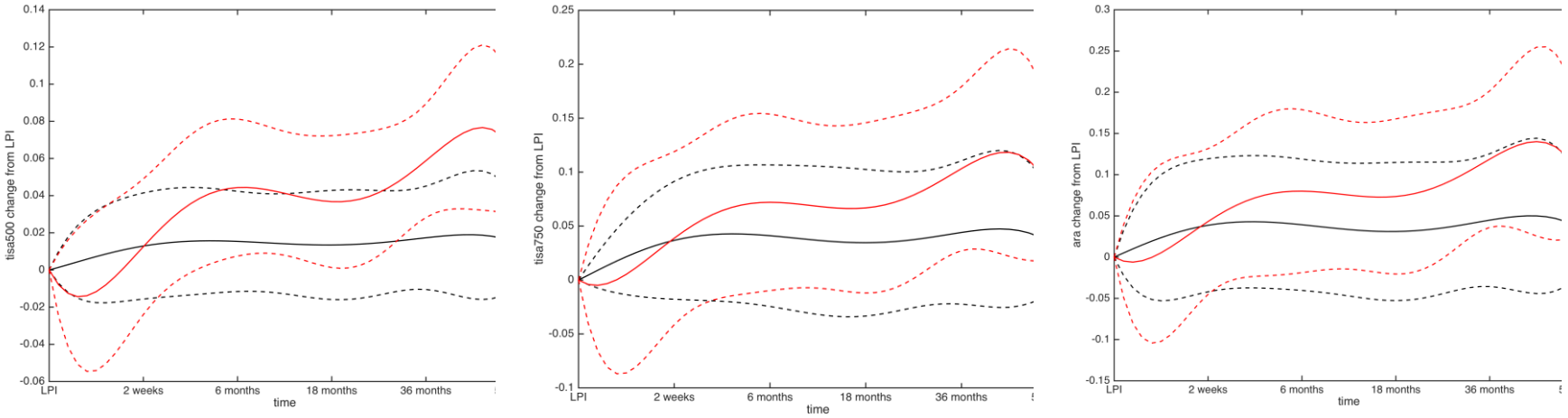
Figure 18 Longitudinal Changes in ARA (ARA: angle recess area, Whiskers in box plots extends to 1.5 times of the interquartile range)



AOD250 **AOD500** **AOD750**

Figure 19 Predicted Mean and 95% CI of the Mixed Effect Models for AOD250, AD500 and AOD750

(AOD: angle opening distance, red lines: treated eyes; black lines: untreated eyes; solid lines: means; dotted lines: limits of 95% CI)



TISA 500 **TISA 750** **ARA**

Figure 20 Predicted Mean and 95% CI of the Mixed Effect Models for TISA500, TISA750 and ARA

(TISA: trabecular iris space area; ARA: angle recess area; red lines: treated eyes; black lines: untreated eyes; solid lines: means; dotted lines: limits of 95% CI)

8. Iris dynamic behaviours of primary angle-closure suspects before and after laser peripheral iridotomy

8.1. Introduction

Based on data from previous population-based prevalence surveys, it is estimated that 10% of elderly Chinese have anatomically narrow anterior chamber angles, and are therefore at significantly increased risk of developing primary angle-closure.[23] Despite of the scarcity of evidence from large-scale natural history studies on asymptomatic suspects, a 5-year observation of a small cohort of asymptomatic suspects reported that up to 22% of PACS developed PAC if no prophylactic measures were taken.[226] There has also been anecdotal estimates that only 1 out every 10 persons with gonioscopically narrow angles will eventually develop significant disease, i.e. PAC or PACG.[246] What is it unique about those eyes that finally develop angle-closure disease? This is a question that has aroused tremendous interest in the area of glaucoma-related research. Considering the factor that the drainage angles of all asymptomatic suspects are gonioscopically narrow, one can hardly associate risks for developing primary angle-closure only with static anatomical features.

Iris, one of the cardinal structures shaping the drainage angle, has been the focus of recent research on dynamic factors that may possibly lead to primary angle-closure. Quigley et al[246] have proposed a theory that the behaviour of the iris tissue in dark illumination may be comparable to a squeezed sponge. When the pupil is dilated either by change in illumination or pharmacological effects, the iris may lose volume due to

loss in extracellular fluid from the stroma. In a small cohort of patients predominantly of European derivation, Quigley and colleagues compared changes in the iris cross-sectional area with pupil size between eyes with angle-closure and open angle glaucoma. All eyes were found to have relatively smaller cross-sectional area of the iris measured in AS-OCT images when the pupil was enlarged physiologically or pharmacologically. Compared to those with open angles, eyes with primary angle-closure had less reduction in iris cross-sectional areas with enlargement of the pupil.[157] The amount of reduction in iris cross-sectional area with pupil dilation was shown to be significantly associated with iris colour. In other words, Quigley's assumption and study findings have shown that iris volume decreases in all eyes with dilation caused by either decrease in illumination or pharmacological mydriatic effect. The differences, or the effect from iris dynamic behaviour differs in the amount of such decrease in iris volume described above. Another previous study by a group of researchers in France, however, came to a very different conclusion. Aptel and colleagues [160] measured volume of the iris (calculated from cross-sectional area of the iris) before and after pharmacological dilation in 30 fellow eyes of patients with unilateral acute primary angle-closure and 30 eyes with wide open drainage angles in age- and sex-matched individuals. Compared to baseline levels, post-dilation iris volume was found to increase in fellow eyes of patients with unilateral acute attacks of angle-closure, whereas the iris volume of eyes with open angles decreased after dilation.

The research described here aims at investigating: (1) the dynamic changes of anterior chamber angle configuration and iris anatomical features with physiological pupil dilation in primary angle-closure suspects of Chinese ethnicity; (2) the influence of LPI on dynamic behaviours of iris tissue; (3) associations of iris dynamic behaviours with drainage angle configurations.

8.2. Methods

ASOCT scans were acquired horizontally in both dark (<1 lux illumination) and light illuminations from PACS eyes. The illumination was calibrated using a digital light meter (Easy View model EAQ30; Extech Instruments, Inc., Waltham, MA, USA). Anatomical features of the anterior chamber angle and the iris were measured quantitatively in AS-OCT images using the Zhongshan Angle Assessment Program [90] (the ZAAP program, Guangzhou, China).

8.2.1. Assessment of angle configurations using AS-OCT

See 3.2 for details.

8.2.2. Assessment of iris configurations using AS-OCT

Anatomical features of the iris were quantitatively measured from AS-OCT scans using the ZAAP program. Five parameters were used for assessing iris configuration: iris cross-sectional area (I-AREA), iris curvature (I-CUVR), and iris thickness (IT750, IT2000).

I-AREA, the measurement of iris cross-sectional area, was calculated as the cumulative area of the left and right cross-sections of the iris from the sclera spur to the pupil margin in AS-OCT scans.[228,247]

See 3.2 for definitions of I-CURV, IT750 and IT2000.

8.2.3. Statistical Analysis

Wilcoxon signed ranks tests were used for comparing quantitative AS-OCT measurements of angle and iris configurations in dark and in light. *P* values less than 0.05 were regarded as indicators for statistical significance. Analyses of associations of iris dynamic changes were performed using univariate and multiple linear regression models. All statistical analyses were performed using Stata/SE 13.1 (StataCorp, College Station, TX, USA).

8.3. Results

8.3.1. Change in Anterior Chamber Angle Configuration with Different Illumination

As shown in **Table 37** and **Table 38**, at baseline, in both men and women, all measurements of drainage angle width (i.e. AOD250, AOD500, AOD750, TISA500, TISA750, ARA) reduced significantly when the illuminative condition changed from light to dark. Similar trends of changes were found 2 weeks after LPI, when the pupillary block was eliminated.

Table 39 compared the magnitude of dynamic changes in angle configuration before and after LPI. At 2 weeks following LPI, the magnitudes of changes in AOD250, AOD500, and AOD750 (i.e. linear measurements of the angle configuration in AS-OCT images) were significantly lower compared to pre-LPI baseline status. This difference was not found in other variables.

8.3.2. Change in iris configuration with different illumination

Table 40 and **Table 41** summarise changes in iris cross-sectional area, iris volume, peripheral iris thickness and mid-peripheral iris thickness from dark to light illumination in treated and untreated eyes before and after LPI. Iris cross-sectional area measurements in dark and light before and after LPI were available for 833 study subjects. At baseline, in both men and women, iris cross-sectional area significantly decreased with physiological dilation of the pupil when the illumination changed from light to dark (all differences were statistically significant). Two weeks after LPI, the relationship between iris cross-sectional area measured in dark and in light remained similar: measurements in light were significantly greater, although the magnitudes of changes seemed to be smaller.

Table 42 compared the magnitudes of change in iris cross-sectional areas in men and women before and after elimination of pupillary block. The magnitudes of changes appeared to be smaller after LPI compared to baseline levels in both men and women. Statistically significant difference was only found in women.

8.3.3. Associations of dynamic changes of iris configuration

Table 43 shows results of univariate and multivariate models for analysing associations of changes in iris cross-sectional area under different illuminative conditions. In both univariate and multivariate linear regression analysis, before laser treatment, greater magnitude of reduction in iris cross-sectional area was significantly associated with younger age and larger pupil diameter in the dark. After LPI, however, only large pupil diameter in the dark was associated with more decrease in iris cross-sectional area from light to dark.

8.3.4. Discussion

In the PACS cohort of the current research, both iris cross-sectional area and iris volume decreased significantly when physiological pupil dilation occurred with changed illumination. Greater magnitude of dynamic changes in iris configuration was significantly associated with larger pupil diameter in dark. Elimination of pupillary block did not change the pattern of iris dynamic behaviours under different illuminations, although the magnitude of dynamic changes in iris configurations reduced slightly but significantly following the elimination of pupillary block.

Results of the current analysis are in accordance with findings of a previous study, giving further supporting evidence to Quigley's hypothesis about the sponge-like characteristic of the iris tissue [246] . Quigley and colleagues [157] reported significantly smaller iris cross-sectional areas in eyes with physiological or pharmacological dilation. Each 1 mm of enlargement in pupil was found to cause a 0.19 mm^2 decrease in iris cross-sectional area. This study had a relatively small sample size of 65 participants, of which 72% were of European derivation and only 4 participants were Asians. Although inter-ethnicity comparison of adequate power was not possible due to the limited sample size, the authors did find an association between brown iris colour and greater iris cross-sectional area. In the current research, all study participants were of Chinese ethnicity, and all eyes belonged to the category of "brown iris colour". Although the nature of this study cohort does not allow comparison of dynamic iris behaviour between different ethnic groups, it does give evidence that the iris of Chinese PACS present with similar dynamic behaviour compared to the iris of angle-closure suspects of European derivation.

In Quigley's study, eyes with closed angles were also found to have smaller magnitude of dynamic changes in iris cross-sectional area, compared to those with open angles.[157] In the PACS cohort of the current research, however, the magnitude of

dynamic changes in iris configuration was not significantly associated with angle width.

Although it is impossible to compare iris dynamic behaviour between eyes with closed and open angles due to the lack of open angle eyes serving as controls in the current study cohort, the study design of the ZAP trial gives us a unique opportunity to compare iris dynamic behaviours in PACS eyes before and after the elimination of pupillary block. The theory behind a possible relationship between LPI and iris dynamic behaviour lies in a presumed change in the intrinsic tension of the iris tissue after the elimination of pupillary block by LPI. In the current analysis, however, the trend for dynamic changes in iris configuration with physiological dilation remained unchanged following interventional treatment, although the magnitude of change slightly but significantly reduced after LPI in both men and women. Based on the possible age-related change in iris tissue [248,249] and accommodation capacity, as well as the potential association between accommodation and pupillary block [250,251], one possible explanation for the association between age and dynamic iris behaviours may be decrease in tissue elasticity of the iris with increased age. Another explanation might be age-related reduction in accommodating capacity, which may result in less significant change in iris configuration from pupillary block. The disappearance of significant associations between age and the magnitude of iris dynamic behaviour after the elimination of pupillary block in the current study, may serve as further supporting evidence for the influence from age, accommodation and pupillary block on iris dynamic behaviours.

Table 37 Changes in Angle Configurations with Illumination before and after LPI† in Men

AS-OCT Measurements	Before LPI† [Median (Interquartile Range)]			¦ Weeks after LPI† [Median (Interquartile Range)]		
	In Dark	In Light	*P* value‡	In Dark	In Light	*P* value‡
Untreated Eyes						
AOD250† (μm)	80.0 (90.5)	133.0 (88.0)	<0.001	87.0 (92.5)	144.0 (85.5)	<0.001
AOD500† (μm)	94.5 (78.5)	159.6 (72.5)	<0.001	99.3 (73.0)	155.0 (63.5)	<0.001
AOD750† (μm)	144.5 (79.0)	215.0 (91.0)	<0.001	143.3 (83.0)	221.0 (82.0)	<0.001
TISA500† (1000μm2)	52.5 (38.5)	82.5 (36.0)	<0.001	54.8 (45.0)	82.0 (39.5)	<0.001
TISA750† (1000μm2)	92.0 (60.0)	142.0 (57.5)	<0.001	94.8 (60.2)	141.5 (54.5)	<0.001
ARA† (1000μm2)	103.5 (74.0)	163.0 (83.0)	<0.001	108.0 (87.0)	162.0 (90.5)	<0.001
Treated Eyes						
AOD250† (μm)	73.5 (92.0)	131.0 (91.0)	<0.001	127.5 (93.5)	174.5 (97.0)	<0.001
AOD500† (μm)	100.5 (80.8)	163.5 (64.5)	<0.001	152.5 (79.0)	209.5 (77.5)	<0.001
AOD750† (μm)	135.3 (78.3)	219.0 (73.5)	<0.001	203.5 (94.5)	302.5 (91.0)	<0.001
TISA500† (1000μm2)	54.3 (44.3)	81.5 (39.0)	<0.001	78.0 (45.5)	135.0 (67.5)	<0.001
TISA750† (1000μm2)	95.3 (58.8)	137.5 (53.5)	<0.001	98.5 (50.0)	174.5 (88.0)	<0.001
ARA† (1000μm2)	106.0 (72.5)	154.5 (84.0)	<0.001	153.0 (96.0)	197.0 (112.0)	<0.001

† LPI: laser peripheral iridotomy; AOD: angle opening distance; TISA: trabecular-iris space area; ARA: angle recess area

‡ *P* values from Wilcoxon signed –rank tests

Table 38 Changes in Angle Configurations with Illumination before and after LPI† in Women

AS-OCT Measurements	Before LPI† [Median (Interquartile Range)]			Weeks after LPI†† [Median (Interquartile Range)]		
	In Dark	In Light	*P* value‡	In Dark	In Light	*P* value‡
Untreated Eyes						
AOD250† (μm)	71.0 (92.0)	123.0 (80.3)	<0.001	72.0 (82.5)	127.7 (88.0)	<0.001
AOD500† (μm)	82.0 (80.5)	146.2 (69.0)	<0.001	84.0 (71.5)	145.3 (66.5)	<0.001
AOD750† (μm)	118.0 (87.0)	191.8 (88.0)	<0.001	125.5 (83.5)	193.8 (83.5)	<0.001
TISA500† (1000μm2)	51.0 (41.5)	74.5 (36.5)	<0.001	51.5 (40.0)	76.3 (37.0)	<0.001
TISA750† (1000μm2)	87.5 (58.5)	127.0 (55.0)	<0.001	86.0 (56.0)	127.8 (55.2)	<0.001
ARA† (1000μm2)	96.5 (72.5)	143.5 (70.5)	<0.001	97.5 (72.5)	144.0 (72.3)	<0.001
Treated Eyes						
AOD250† (μm)	70.5 (94.5)	123.3 (88.5)	<0.001	107.8 (95.0)	158.0 (98.5)	<0.001
AOD500† (μm)	84.0 (69.5)	140.3 (73.0)	<0.001	134.5 (79.0)	191.5 (76.5)	<0.001
AOD750† (μm)	128.0 (83.0)	189.3 (88.5)	<0.001	191.5 (87.5)	281.0 (109.0)	<0.001
TISA500† (1000μm2)	49.5 (38.5)	74.0 (38.8)	<0.001	67.5 (42.0)	92.0 (47.0)	<0.001
TISA750† (1000μm2)	86.0 (55.5)	125.2 (57.5)	<0.001	116.8 (60.5)	163.5 (74.5)	<0.001
ARA† (1000μm2)	95.5 (69.5)	140.8 (80.3)	<0.001	129.8 (77.0)	184.0 (106.5)	<0.001

† LPI: laser peripheral iridotomy; AOD: angle opening distance; TISA: trabecular-iris space area; ARA: angle recess area

‡ *P* values from Wilcoxon signed –rank tests

Table 39 Magnitude of Dynamic Change in Angle Configuration with Illumination

AS-OCT Measurements	Men (%)§			Women (%)§		
	Before LPI†	After LPI†	*P* value‡	Before LPI†	After LPI†	*P* value‡
Untreated Eyes						
AOD250† (μm)	45.3 (46.6)	33.9 (52.8)	0.16	42.7 (54.1)	43.2 (52.2)	0.66
AOD500† (μm)	39.7 (42.5)	36.0 (40.0)	0.59	42.1 (41.7)	42.5 (41.3)	0.65
AOD750† (μm)	38.7 (31.6)	36.3 (29.0)	1.00	39.1 (31.8)	39.2 (31.4)	0.90
TISA500†(1000μm^2)	35.1 (35.4)	33.1 (34.3)	0.86	33.4 (39.9)	33.4 (39.9)	0.86
TISA750† (1000μm^2)	34.5 (29.9)	32.2 (33.6)	0.93	32.3 (37.1)	33.1 (34.6)	0.46
ARA†(1000μm^2)	36.0 (35.2)	33.2 (37.3)	0.99	32.5 (39.3)	33.6 (39.5)	0.58
Treated Eyes						
AOD250† (μm)	43.3 (61.4)	31.5 (43.1)	0.15	38.7 (57.3)	34.6 (46.6)	0.041
AOD500† (μm)	38.3 (39.7)	30.4 (31.0)	0.015	40.2 (40.4)	32.8 (33.3)	<0.001
AOD750† (μm)	37.8 (29.8)	31.1 (25.9)	0.004	37.2 (31.4)	33.4 (23.6)	<0.001
TISA500† (1000μm^2)	31.5 (40.5)	24.9 (37.8)	0.13	31.4 (37.9)	28.6 (35.1)	0.08
TISA750† (1000μm^2)	31.9 (34.9)	25.5 (35.7)	0.13	32.2 (35.1)	28.2 (30.7)	0.051
ARA† (1000μm^2)	30.2 (37.1)	26.0 (40.6)	0.12	33.4 (37.1)	28.4 (35.0)	0.03

§ The magnitude of dynamic change in angle configuration=[(measure in light-measure in dark)/measure in light]*100%

† LPI: laser peripheral iridotomy; AOD: angle opening distance; TISA: trabecular-iris space area; ARA: angle recess area

‡ *P* values from Wilcoxon signed –rank tests

Table 40 Dynamic Changes in Iris Configuration in Treated and Untreated Eyes before and after LPI† in Men

	Before LPI† [Median (Interquartile Range)]			**2 Weeks after LPI†** [Median (Interquartile Range)]		
AS-OCT Measurements	**In Dark**	**In Light**	***P* value‡**	**In Dark**	**In Light**	***P* value‡**
Untreated Eyes						
Iris Cross-sectional Area (mm^2)	1.59 (0.29)	1.84 (0.32)	<0.001	1.55 (0.30)	1.84 (0.36)	<0.001
Iris Curvature (mm)	0.40 (0.13)	0.41 (0.15)	0.60	0.38 (0.15)	0.41 (0.16)	0.002
IT750† (mm)	0.50 (0.12)	0.48 (0.12)	<0.001	0.44 (0.12)	0.43 (0.13)	<0.001
IT2000† (mm)	0.50 (0.11)	0.47 (0.10)	0.001	0.50 (0.11)	0.47 (0.09)	0.06
Pupil Diameter (mm)	4.37 (1.06)	2.59 (0.75)	<0.001	4.32 (1.01)	2.59 (0.70)	<0.001
Treated Eyes						
Iris Cross-sectional Area (mm^2)	1.58 (0.30)	1.87 (0.33)	<0.001	1.56 (0.29)	1.77 (0.48)	<0.001
Iris Curvature (mm)	0.38 (0.14)	0.39 (0.16)	0.65	0.23 (0.13)	0.20 (0.16)	0.19
IT750† (mm)	0.49 (0.13)	0.48 (0.10)	<0.001	0.43 (0.12)	0.42 (0.11)	<0.001
IT2000† (mm)	0.48 (0.11)	0.46 (0.08)	<0.001	0.49 (0.11)	0.47 (0.14)	0.04
Pupil Diametre (mm)	4.35 (1.01)	2.64 (0.72)	<0.001	4.28 (0.99)	2.51 (0.48)	<0.001

† LPI: laser peripheral iridotomy; IT: iris thickness

‡ *P* values from Wilcoxon signed –rank tests

Table 41 Dynamic Changes in Iris Configuration in Treated and Untreated Eyes before and after LPI† in Women

	Before LPI† [Median (Interquartile Range)]			**2 Weeks after LPI†** [Median (Interquartile Range)]		
AS-OCT Measurements	**In Dark**	**In Light**	***P* value‡**	**In Dark**	**In Light**	***P* value‡**
Untreated Eyes						
Iris Cross-sectional Area (mm^2)	1.56 (0.31)	1.86 (0.36)	<0.001	1.55 (0.31)	1.88 (0.38)	<0.001
Iris Curvature (mm)	0.40 (0.13)	0.40 (0.13)	0.46	0.40 (0.13)	0.40 (0.15)	0.30
IT750† (mm)	0.48 (0.11)	0.44 (0.11)	<0.001	0.48 (0.12)	0.44 (0.11)	<0.001
IT2000† (mm)	0.50 (0.09)	0.47 (0.09)	<0.001	0.50 (0.09)	0.48 (0.10)	<0.001
Pupil Diametre (mm)	4.45 (0.91)	2.67 (0.64)	<0.001	4.48 (0.93)	2.64 (0.66)	<0.001
Treated Eyes						
Iris Cross-sectional Area (mm^2)	1.57 (0.28)	1.86 (0.38)	<0.001	1.55 (0.34)	1.79 (0.40)	<0.001
Iris Curvature (mm)	0.40 (0.12)	0.40 (0.14)	0.42	0.24 (0.14)	0.19 (0.13)	<0.001
IT750† (mm)	0.48 (0.11)	0.43 (0.12)	<0.001	0.47 (0.11)	0.43 (0.13)	<0.001
IT2000† (mm)	0.50 (0.10)	0.48 (0.08)	<0.001	0.51 (0.09)	0.47 (0.10)	<0.001
Pupil Diametre (mm)	4.43 (0.96)	2.75 (0.66)	<0.001	4.40 (0.99)	2.67 (0.67)	<0.001

† LPI: laser peripheral iridotomy; IT: iris thickness

‡ *P* values from Wilcoxon signed –rank tests

Table 42 Magnitude of Dynamic Change in Iris Anatomy with Illumination in Treated Eyes

	Men (%)§			Women (%)§		
	Before LPI	2 Weeks After LPI†	*P* value‡	Before LPI	2 Weeks After LPI†	*P* value‡
Untreated Eyes						
Iris Cross-sectional Area (mm^2)	14.4 (10.9)	14.3 (10.1)	0.78	16.0 (11.0)	16.8 (11.8)	0.16
Iris Curvature (mm)	1.0 (37.0)	5.4 (31.3)	0.08	-0.5 (34.8)	1.1 (31.0)	0.35
IT750† (mm)	-7.5 (25.0)	-8.1 (25.0)	0.98	-11.1 (25.9)	-8.6 (27.7)	0.07
IT2000† (mm)	-5.7 (17.1)	-2.3 (19.2)	0.29	-5.5 (17.4)	-5.4 (17.6)	0.55
Treated Eyes						
Iris Cross-sectional Area (mm^2)	14.3 (10.1)	12.5 (11.4)	0.12	15.0 (10.9)	14.2 (12.9)	0.006
Iris Curvature (mm)	1.7 (33.6)	-4.6 (74.4)	0.07	1.4 (31.1)	-14.2 (84.1)	<0.001
IT750† (mm)	-10.1 (23.3)	-12.3 (18.5)	0.59	-10.0 (25.8)	-11.0 (26.8)	0.28
IT2000† (mm)	-5.9 (15.1)	-6.6 (19.7)	0.44	-5.3 (16.6)	-6.7 (19.3)	0.16

† LPI: laser peripheral iridotomy; IT: iris thickness

‡ *P* values from Wilcoxon signed –rank tests

§ The magnitude of dynamic change in angle configuration=[(measure in light-measure in dark)/measure in light]*100%

Table 43 Associations of Changes in Iris Cross-Sectional Area§ with Illumination

	Regression Coefficient	
	Before Treatment	**2 Weeks after Treatment**
Univariate Analysis		
Age	-0.37*	-0.15
Sex	1.27	1.43
Pupil Diameter in Dark	0.19**	0.15**
Baseline Angle Width (°)	0.04	-0.06
Central Anterior Chamber Depth	-1.58	4.14
Axial Length	0.38	-0.31
Body Height	-0.05	0.02
Body Mass Index	0.14	0.41
Multivariate Model†		
Age	-0.42**	-0.15
sex	1.93	2.11
Pupil Diameter in Dark	0.19**	0.15**
Baseline Angle Width (°)	0.14	-0.07
Central Anterior Chamber Depth	-3.52	4.04
Axial Length	1.77	-0.21

§ magnitude of changes in iris cross-sectional area=iris cross-sectional area in light – iris cross-sectional area in dark

* $P<0.05$, ** $P<0.01$

† Independent variables of the multivariate model include: pupil diameter in dark, baseline angle width, age and sex

9. Changes in Intraocular Pressure of Primary Angle-closure Suspects after Laser Peripheral Iridotomy

9.1. Introduction

Despite being less prevalent than POAG, PACG accounts for nearly half of glaucoma blindness.[1] Although PACG can present as acute angle-closure attacks, the majority of primary angle-closure disease cases are clinically asymptomatic.[2-4] In China alone, the estimated number of asymptomatic people at risk of angle-closure is up to 28 million.[5]

Although IOP is not considered a diagnostic criterion for glaucoma, it has an undisputable relationship with risks of onset and progression of glaucoma.[6-8] In the classification proposed by the International Society Geographical & Epidemiological Ophthalmology (ISGEO)[9] and confirmed by the World Glaucoma Association[10], primary angle-closure diseases are categorised into 3 classes: PACS, PAC and PACG. According to this classification, IOP is used to differentiate disease from an innocuous rare finding and to identify the onset of angle-closure disease. There have been few studies of sufficient power to assess whether subtle abnormalities of structure or function exist in PACS. However, I noted from work of Vijaya et al[11] in south India that

unadjusted mean IOP was higher in people with PACS than in a “normal” population. With limited evidence available, the characteristics of IOP in PACS are still poorly understood. Insight into the association between IOP (even if the IOP is within the normal range) and angle width in these “suspects” may help reveal some early compromise in aqueous drainage capacity.

This analysis therefore aimed to investigate the association between IOP and the anatomic configuration of anterior chamber angle in asymptomatic people with gonioscopically-evident narrow drainage angles.

9.2. Methods

See 3.1.3 for detailed methodology for IOP measurement, gonioscopy, AS-OCT quantitative analysis and measurement of anthropometric variables.

IOP of the left eye of each participant were used for statistical analysis. Student t tests were used for comparison of age-specific IOP levels between male and female participants. The tests for trend across ordered groups were used to examine the trend of IOP levels between participants of different age groups or different Shaffer grades. Univariable and multivariable linear regression models were used to examine associations between IOP and angle width assessed both under gonioscopy and by AS-OCT images. All statistical analysis was performed using Stata/SE 13.1 (StataCorp,

College Station, TX, USA).

9.3. Results

A total of 889 participants (mean age: 59.3±5.0 years) were identified as being eligible to participate in the ZAP trial. The mean IOP of all participants was 14.8±2.9 mmHg. Men and women of all age groups were not found to differ significantly in IOP (**Table 44**). No obvious trends were observed between IOP levels of different age groups either.

Eyes with lower mean Shaffer grades tended to have higher IOP (**Table 45**). A test for linear trend for higher IOP with decreasing angle width was statistically significant. In univariable analyses, IOP was significantly associated with angle width estimated using gonioscopy as well as quantitative measures in AS-OCT images, i.e. AOD_{250}, AOD_{500}, AOD_{750}, $TISA_{500}$, $TISA_{750}$ and ARA (**Table 46**). These associations remained significant following adjustment for age, sex, axial length, body height, BMI, systolic blood pressure, education level and income level .

9.4. Discussion

We found a significant association between higher IOP and narrower angle width

among individuals with narrow angles using both gonioscopy and quantitative measures from AS-OCT images. These findings suggest that asymptomatic angle-closure, even with eye pressures in the “normal range” may lead to subclinical impairment of trabecular meshwork function. This may be the result of subtotal appositional iridotrabecular contact, causing physical obstruction of the trabecular meshwork, or it could be due to damage to the trabecular meshwork. Reports on patients with PACG identified pathological changes in drainage angles both with and without PAS including: deposition of homogenous material covering the surface of trabeculae or blocking the orifices between trabeculae; disorganisation, degeneration and loss of trabecular endothelium; loss of regularity in trabecular architecture; as well as increased phagocytosis of pigment granules.[252-256]

There is a recognised association between established angle pathology and higher IOP.[77,78,257] One previous study found that IOP increased across the spectrum of angle-closure disease with those with PACS having the lowest IOP, those with PAC having higher IOP and those with PACG having the highest IOP.[257] In patients with chronic PACG, higher IOP was seen in those with narrower angles and greater extent of PAS.[258]Additionally, a population-based study in Singapore reported a small but significant association between higher IOP and narrower angle width[78], suggesting some impairment in aqueous outflow in eyes without visible pathology in the drainage angles. In the ISGEO glaucoma classification system[259], elevated IOP is used to differentiate people with angle-closure disease from those at risk of angle-closure.

However, “normal IOP” is a statistically-derived concept. There is no evidence that “statistically normal IOP” definitely proves normal, unimpaired aqueous drainage function.

The mean IOP of the PACS cohort in the current study was lower than the value reported from a prevalence study in south India (15.3±4.2 mmHg) [18], where the IOP was also measured using Goldmann applanation tonometry. A previous population-based survey in north China [257] reported a mean IOP (14.7±2.6 mmHg) in PACS measured with Perkins applanation tonometry[260], which is similar to the current study. No significant trend was observed for IOP to rise or fall with increasing age. This may be due primarily to the inclusion criteria which limited the age span from 50 to 70. Part of the reasons might also be the incapability of cross-sectional observations to fully represent longitudinal trends [261].

Lens-related factors may offer another possible explanation for the association between higher IOP and narrower drainage angles in PACS. Lens vault measured in AS-OCT images, a novel parameter representing the surface contour of the anterior portion of the lens, was recently reported to be independently associated with angle-closure.[162] Patients of various ethnicities with primary angle-closure diseases have been shown to have significantly greater lens vault than those with open angles.[262] Lens removal has been shown to result in a statistically significant decrease in IOP of asymptomatic suspects with gonioscopic narrow angles, which was in accordance with

widening of the drainage angles.[263] These findings may provide support to the previous hypothesis that lens position influences trabecular meshwork functional architecture, as well as the lumen size of the Schlemm canal.[264,265] Results of the current study may add further evidence to the above findings. Lens vault was shown to be significantly associated with IOP in univariable regression analysis. When Shaffer grades, AOD_{250}, $TISA_{500}$ and ARA were adjusted separately in multivariable model (together with other factors, i.e. age, sex, axial length, height, body mass index, systolic blood pressure, education level and income level), the association between lens vault and IOP remained significant (**Table 46**).

The strength of our study lies in the large sample size of a PACS cohort recruited in a single study site with a highly standardised protocol. IOP values of all participants were measured using Goldmann applanation tonometry. However, caution is warranted when interpreting findings of the current study. A few potential limitations are worthy of note. Participants in the present study were recruited for a randomised clinical trial with an eligibility criterion of age being 50 to 70 years. This limits the generalisability of our findings to younger populations. Second, although study participants of the ZAP trial were recruited from the general community, the data from those who gave consent to participate might not be representative of those who were identified as being eligible but declined participation. However, we did compare participants in the current study (N=889) to those PAC suspects identified as eligible who declined participation (N=37) on variables including: age, sex, IOP, Shaffer grades, axial length, BMI, systolic blood

pressure, education level and income level and no statistically significant differences were found (data not shown).

In summary, this study of primary angle-closure suspects demonstrated higher IOP in participants with narrower anterior chamber angle width assessed by both gonioscopy and AS-OCT. Our findings support the results of other similar studies and expand the list of factors that determine intraocular pressure - the sole proven modifiable risk factor for glaucoma. Further, these findings point towards a graduated increase in risk of pressure elevation in people with narrow angles, without a clear threshold effect.

Table 44 Age-specific Goldmann Applanation Intraocular Pressure in Men and Women

Age	Men		Women		*P* value§
	IOP† [mmHg, Mean(95% CI)]	N	**IOP**† [mmHg, Mean(95% CI)]	N	
50-54	13.6 (12.2, 15.1)	19	14.9 (14.5, 15.3)	190	0.048
55-59	14.9 (13.9, 15.9)	39	15.0 (14.7, 15.4)	251	0.82
60-64	14.8 (14.0, 15.6)	52	14.7 (14.3, 15.1)	199	0.86
65-70	14.9 (13.9, 15.9)	42	15.2 (14.6, 15.8)	97	0.57
Total	14.7 (14.2, 15.2)	152	14.9 (14.7, 15.1)	737	0.37
Test for Trend	*P*=0.29		*P*=0.92		

† IOP: intraocular pressure; § P values from Student t tests for inter-gender comparison

Table 45 Intraocular Pressure and Anterior Chamber Angle Configuration

Mean Shaffer Grades	**Intraocular Pressure** (mmHg, [Mean (95%CI)])		
	All (N=889)	**Men** (N=152)	**Women** (N=737)
0~0.25	15.6 (15.0, 16.3)	16.0 (13.3, 18.7)	15.6 (14.9, 16.3)
0.5~0.75	14.9 (14.5, 15.4)	15.2 (13.7, 16.6)	14.9 (14.4, 15.4)
1~1.25	14.9 (14.6, 15.3)	15.0 (13.9, 16.2)	14.9 (14.5, 15.3)
1.5~1.75	14.9 (14.6, 15.3)	15.0 (14.1, 15.8)	14.9 (14.6, 15.3)
≥2	14.3 (13.9, 14.8)	13.7 (12.7, 14.6)	14.6 (14.1, 15.1)
Test for trend across ordered groups	*P*=0.007	*P*=0.029	*P*=0.065

Table 46 Univariate and Multivariate Regression Analyses of the Association between IOP† and Angle configuration

	Univariate Regression Models		Multiple Regression Models*	
	Regression Coefficient (R-squared (%))	*P* value	Regression Coefficient (R-squared (%))	*P* value
Angle Width (per 10°)	-0.05 (0.80)	0.009	-0.08 (6.90)	<0.001
AOD_{250} (mm)†	8.12 (1.77)	0.001	8.33 (5.78)	0.001
AOD_{500} (mm)†	9.45 (3.49)	<0.001	10.64 (8.28)	<0.001
AOD_{750} (mm)†	5.56 (2.09)	<0.001	6.41 (6.58)	<0.001
$TISA_{500}$ (mm)†	15.67 (1.88)	0.001	16.71 (6.06)	0<0.001
$TISA_{750}$ (mm)†	4.51 (1.21)	0.005	4.34 (5.01)	0.009
ARA(mm)†	3.46 (1.03)	0.010	3.40 (4.90)	0.013
Lens Vault (mm)	1.58 (1.86)	0.001	1.50 (5.54)	0.001

*Variables adjusted for in multiple regression models: age, sex, axial length, height, body mass index, systolic blood pressure, education level and income level and central corneal thickness

† IOP: Intraocular pressure; AOD, angle opening distance; TISA, trabecular iris space area; ARA, angle recess area

10. Summary, Conclusions & Future Directions

Primary angle-closure glaucoma, a condition affecting one third of the current estimated 60 million glaucoma patients in the world, is characterised by a worse visual prognosis compared to POAG, if undiagnosed and untreated. It is projected that by the year 2020, up to 11.2 million people will be blinded bilaterally by glaucoma. Despite the much lower prevalence compared to POAG, PACG is responsible for nearly half of the binocular glaucoma blindness. Although PACG was initially recognised as acute and dramatic episodes of IOP elevation due to sudden and extensive closure of the drainage angle, more recent research has shown that the majority part of PACG is presented in a chronic asymptomatic form. [5-8,266] According to findings from previous population-based study, nearly 1 in 10 elderly urban Chinese aged 50 or above have anatomically narrow anterior chamber angles evident on gonioscopy.[23] This condition, defined in the ISGEO classification [2] as “primary angle-closure suspect”, is the first stage in a spectrum of conditions including primary angle-closure and primary angle-closure glaucoma. It is still unclear what proportion of angle-closure suspects go on to develop established angle-closure or angle-closure glaucoma, and what features or factors precipitate or promote such progression.

Although recent research has suggested that non-pupil block mechanisms may play very important roles in a considerable proportion of cases with angle-closure, pupil block is still believed to be the predominant mechanism in primary angle-closure. The

relative obstruction to free flow of aqueous across the lens-iris diaphragm results in a pressure gradient, with greater pressure behind the iris. This results in an anterior iris convexity, which, in anatomically predisposed eyes, brings the iris into contact with the trabecular meshwork outflow channels. The mainstay of treatment, laser peripheral iridotomy (LPI), aims to eliminate this pressure gradient. This then results in flattening of the peripheral iris and consequent widening of the drainage angels, allowing normal aqueous outflow to resume. In theory, the elimination of pupil block should be very effective in preventing angle-closure. In fact, LPI is proven in previous research to be effective in preventing acute attacks of angle-closure in the fellow eyes of patients who suffered acute primary angle-closure in only one eye [185,186] . Subsequent questions of interest are then: Do we really have to "wait" until the onset of acute angle-closure with irreversible tissue damage and dysfunction occurs in one eye, or even both eyes? Can we use LPI as a prophylactic treatment to prevent primary angle-closure suspects from developing established angle-closure disease or angle-closure glaucoma? To address these questions, the ZAP trial, was started in 2008.[74] This large-scale randomised controlled clinical trial aimed to asses the efficacy and safety of LPI when it is used as a prophylactic measure. The seeting for this trial was a large cohort of people with high-risk ocular biometric characteristics age over 50 years living in Guangzhou, southern China. The current PhD project was designed primarily around one main research question: What were the changes in anterior chamber angle configuration in primary angle-closure suspects following prophylactic LPI? Specifically, my research aimed to: (1) Describe of the main anatomical characteristics of primary angle-closure suspects;

(2) Assess of anatomical features of PACS eyes that might contribute to persistent narrow angles following LPI; (3) Investigate the role of dynamic features in the iris, in occlusion of the anterior chamber angle.

In the ZAP trial study participants, compared to age-matched men, women had significantly narrower drainage angles and greater extent of appositional angle-closure. Findings in the current study are in agreement with findings of previous population-based research in elderly urban Chinese aged 50 to 70 years. Based on data from both the ZAP trial and this previous population-based prevalence survey in the same geographic area (i.e. the Liwan Eye Study [23]), several common themes are evident; Shallower central ACD was shown to be significantly associated with both the presence of PACS and narrower angle width, quantitatively measured in anterior segment OCT (AS-OCT) images. Individuals with lower body weight and lower body height were found to be more likely to have narrow anterior chamber angles. Lower BMI was significantly associated with greater risk for narrow angle after adjusting for confounding factors including height, age, sex, central ACD and axial length. This association was shown to be significant only in women in sex-stratified multivariate analysis. Dynamic iris behaviour (e.g. changes of iris thickness and volume under different illumination) of the iris may also play an important role in the association between BMI and angle configuration, since variations in BMI have recently been associated with different dynamic changes of the pupil.[18] The mechanism of this association between lower BMI and dynamic characteristics of the thickness and

volume of peripheral iris under dark illumination remains to be determined. This requires further research to clarify the nature of this association.

Qualitative grading of UBM images was used to assess characteristics of the anterior segment structures related to angle configuration, to investigate anatomical features that may determine the efficacy of prophylactic LPI in PACS eyes,. The assessment was carried out using a qualitative grading system I described in a published previous research.[84] Compared to eyes with wide-open angles after LPI, eyes with persistently occludable angles after LPI were found to have a thicker iris overall, a relatively more bulky peripheral iris, a more anteriorly inserted iris, and more anteriorly-positioned ciliary processes. These findings confirm the results of previous quantitative research (ref MGH UBM paper), and show that a qualitative assessment of UBM images may be as clinically useful as quantitative analysis of key qualitative features in UBM scans. Further qualitative and quantitative research on PACS eyes with persistently narrow angles following LPI will be important to verify this belief and possibly develop a risk prediction algorithm based on qualitative assessment.

Immediate and long-term changes in angle configurations of PACS eyes after LPI were also assessed in the current project. An overall trend of significant narrowing of the anterior chamber angle over time in both treated and untreated eyes from 2 weeks to 18 months post-LPI was observed. The magnitude of decrease in angle width over time was significantly more pronounced in eyes without prophylactic LPI. Although

there was some fluctuation in angle width, the trend was for angles to narrow down until 54 months post-LPI. The long-term trend of narrowing of drainage angles in PACS eyes both treated and untreated by LPI suggests the existence of other important factors that cannot be entirely eliminated or controlled by LPI. Further long-term observation is needed to determine: (1) how the longitudinal changes in angle-configuration of treated and untreated PACS eyes differ; (2) whether the changes in angle configuration in treated eyes are of real clinical significance.

In addition to the above observations on static anatomical features affecting angle configurations, dynamic changes in the iris which occur with physiological pupil dilation were also assessed. A significant decrease in iris cross-sectional area with physiological dilation of the pupil when the illumination changed from light to dark was observed in PACS eyes of both men and women. Two weeks after LPI, the relationship between iris cross-sectional area measured in dark and in light remained similar: measurements in light were significantly greater, although the magnitudes of changes seemed to be smaller. These findings support Quigley's assertions of the sponge-like characteristic of iris tissue,[246] which was suggested by his finding of significantly smaller iris cross-sectional areas in eyes with physiological or pharmacological dilation in a relatively small sample of patients with open angle glaucoma or angle-closure.[157] The slight but significant difference in iris dynamic behaviour after LPI may suggest associations between pupillary block, tensions within iris tissue and iris dynamic behaviours. Further evidence from anatomical, mechanical and histological studies are

needed to achieve a better understanding of these potential associations.

Primary angle-closure suspects with the narrowest anterior chamber angles (assessed by both gonioscopy and AS-OCT) have higher IOPs. Findings in this research support the results of other similar studies, and expand the list of factors that determine intraocular pressure - the sole proven modifiable risk factor for glaucoma. Further, these findings point towards a graduated increase in risk of pressure elevation in people with narrow angles, without a clear threshold effect.

In conclusion, among participants recruited from screening a large community based cohort of elderly people in southern China, we have confirmed the association of well-documented biometric risk factors for angle-closure, and again shown that the majority of people (82%, at post-LPI 18 months) undergoing LPI will have wider angles after treatment than before. Important novel findings are that

- LPI has an effect on the dynamic features of the iris, and results in a significant decrease in iris cross-sectional area with physiological dilation of the pupil.
- There is a continued narrowing of the angles with age. This is more pronounced in eyes that have not had LPI, but is seen in treated eyes as well.
- A qualitative assessment of UBM images will give some idea of the likely outcome of LPI, allowing ophthalmologists to predict to some degree the outcome of treatment.

Further research is required to verify these novel findings. Further, the results of the

ZAP trial are eagerly awaited and will have a significant impact on the way that PACS patients are treated by ophthalmologists around the world.

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